Hepatic Inflammation and Immunity: A Summary of a Conference on the Function of the Immune System Within the Liver

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Although the liver has been the focus of intensive investigation in many different fields of study, this largest visceral organ of the body has received only scant attention from immunologists until recently. Relatively little is known about the mechanisms underlying the immune responses that are generated during infection of the liver and how these lead to hepatic inflammation. Nor is there a good understanding of how the delicate balance between tolerance and immune recognition is maintained in an organ that is continuously perfused with foreign antigens derived from the gut. Nonetheless, the consequences of inadequate or inappropriate intrahepatic immune responses figure prominently among the diseases treated by hepatologists, in the form of chronic viral infections or autoimmune types of liver disease. The increasing importance of liver transplantation as a means of rescue from otherwise fatal cirrhosis also highlights the need for a better understanding of the mechanisms of immune recognition and the activation of immune lymphocytes within the liver. To address these issues in a multidisciplinary fashion, a meeting was convened of clinical hepatologists, cell biologists, virologists, and those interested in transplant biology, as well as immunologists to discuss the fundamental mechanisms underlying hepatic inflammation and immunity (January 15-17, 1999, Galveston Island, TX).

THE ROLE OF NORMAL LIVER PHYSIOLOGY IN INTRAHEPATIC IMMUNE RESPONSES

The conference began with a review of the functional and structural properties that distinguish the liver from other organs of the body (I. Arias, Boston, MA). Although important and likely to be relevant to the immunology of the liver, they are seldom considered by immunologists. The liver is the only organ that receives a dual blood supply, one from the hepatic arteries and the other from the portal veins draining the intestines, pancreas, and spleen. This unique circulation allows molecules absorbed by the intestine to transit through the liver where they are metabolized or degraded if toxic. The liver metabolizes and/or secretes a number of serum proteins, lipoproteins, lipid-soluble molecules, steroids, and carbohydrates as well as producing bile and urea. Because it is the major primary site of detoxification for the body and acts as a first line of defense against infectious, toxic, or carcinogenic agents arriving from the gut, the liver has evolved mechanisms that allow it to regenerate very quickly if injured. Upon injury, both parenchymal and bile duct tissue regenerate to recreate functional hepatic tissue (I. Arias). Proinflammatory cytokines, including tumor necrosis factor α (TNF-α) and TNF-inducible cytokines such as interleukin 6 (IL-6), play an important role in experimental regeneration of the liver in partially hepatectomized rats (A. M. Diehl, Baltimore, MD), indicating a close linkage between intrahepatic immune responses, inflammation, and hepatic regeneration.

The architecture of the liver is optimized to favor blood/cell plasma exchange. One of the most unusual features of the hepatic tissue is the structure of its endothelium, formed by fenestrated endothelial cells lining the sinusoids and replacing the basement membrane. Fenestrae appear to be dynamic, contracting or dilating in response to different molecules (I. Arias). These 120-nm diameter holes could play an important role in immune responses because they provide a means by which hepatocytes may directly contact lymphocytes circulating in the blood, an important step in the initiation of a primary T-cell immune response. Besides hepatocytes, several nonparenchymal cell types are found within the sinusoids. These include liver-resident lymphocytes, about which surprisingly little is known, macrophages (Kupffer cells), and stellate (or Ito) cells. All of these different cell types may be involved in establishing immunity and/or tolerance, perhaps through interactions with circulating lymphocytes. Moreover, the activation of stellate cells plays a central role in the fibrotic response to inflammation within the liver (D. M. Bissell, San Francisco, CA). These and other aspects of liver physiology and pathology contribute to the liver's status as a unique organ in terms of both its suitability for transplantation and as a frequent site of persistent viral infection.

THE POOL OF INTRAHEPATIC LYMPHOCYTES

The meeting participants agreed that the liver contains a significant number of resident lymphocytes. However, the total number of intrahepatic lymphocytes (IHLs) that can be isolated from a normal adult liver was a matter of considerable debate. Numbers ranged from 10^9 to 10^{11} cells for a

Abbreviations: TNF, tumor necrosis factor; IL, interleukin; IHL, intrahepatic lymphocyte; HCV, hepatitis C virus; NK, natural killer; TCR, T-cell receptor; MHC, major histocompatibility complex; CTL, cytotoxic T lymphocyte; DC, dendritic cell; HBV, hepatitis B virus.

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normal human liver, whereas the total number of lymphocytes in the human body approximates 10^{12} cells (S. Abrignani, Siena, Italy; C. O'Farrelly, Dublin, Ireland).[1] Estimates for the normal mouse liver vary between 10^6 to 10^7 cells (I. N. Crispe, New Haven, CT).[2] It is likely that these differences in numbers result from the use of different purification protocols to isolate the cells (I. N. Crispe). The number of IHLs is increased in patients who are persistently infected by hepatitis C virus (HCV) (S. Abrignani)[3] or in mice infected by adenovirus (G. Dennert, Los Angeles, CA).[4] In HCV-infected livers, most IHLs are found in the G0/G1 state of the cell cycle, suggesting that T-cell activation and expansion occurs outside of the liver, in lymphoid organs, followed by migration of the cells to the liver (S. Abrignani).[3]

Besides natural killer (NK) cells and γδ T-cell receptor (TCR) cells, which comprise at least 15% of the total human IHL pool (C. O'Farrelly), most liver-resident lymphocytes express an αβ TCR. αβ TCR cells can be subdivided into 2 different subsets. Approximately 50% of αβ TCR cells correspond to conventional T lymphocytes expressing high levels of CD3 and coexpressing either CD4 or CD8 α/β coreceptors. The remaining cells belong to an unusual subset expressing lower levels of CD3 than conventional T cells (T. Abo, Niigata, Japan).[5] These nonconventional T cells are either $CD4^-CD8^-$ or coexpress CD4 or CD8 α/α markers (T. Abo, C. O'Farrelly). In the mouse liver, a significant proportion of $CD4^-CD8^-$ and CD4 cells belonging to this unusual subset also express the NK1 marker usually expressed on NK cells and are thus known as NK T cells. They can readily secrete high levels of IL-4 but also IL-2, TNF-α, and interferon gamma on activation. The human equivalent of the mouse NK T cell seems to be the CD56 lymphocyte (C. O'Farrelly).[6] Besides the liver, NK T cells are found with a high frequency in the thymus and bone marrow, and their maturation and recognition are dependent on the monomorphic major histocompatibility complex (MHC) class I molecule CD1 (A. Bendelac, Princeton, NJ). It has recently been shown that α-galactosylceramide activates murine[7] and human[8] NK T cells, implying that NK T cells recognize CD1 associated with glycolipids. MHC class II–deficient mice, which are deficient in conventional CD4 T cells but enriched in CD1-specific T cells, have 2 types of nonconventional CD4 T cells in the spleen. Those expressing NK1.1 have a restricted TCR repertoire using Vβ8.2, Vβ2, or Vβ7 TCR β chains associated with an invariant TCR α chain, Vα14Jα281, while those that are $NK1.1^-$ use Vα3 and Vα8 rather than Vα14. A mutated form of CD1 that is not able to recycle into the endosomes is recognized by T cells bearing Vα3 or 8 but not by Vα14 T cells, suggesting that the migration of CD1 into the endosomal compartment is important for recognition of CD1 by murine CD4 NK1.1 Vα14 T cells (A. Bendelac).[9]

Although conventional T cells in the liver appear to be derived from the periphery, the origin of the nonconventional T cells was a matter of debate during the conference. The liver is the most important hematopoietic organ during fetal life. Although this function is drastically reduced in adults, early CD34 CD45 lymphoid progenitors can still be found in a normal human adult liver (C. O'Farrelly).[10] Furthermore, recombination-activating gene 1 and 2 messenger RNAs as well as preTα messenger RNA, all of which are required for T-cell differentiation, can be detected in intrahepatic T cells (C. O'Farrelly), suggesting that some T cells can differentiate extrathymically.[11] However, the presence of intrahepatic T cells in thymus-deficient nude mice, as well as in thymectomized and bone marrow-reconstituted chimeric mice, was controversial (T. Abo, A. Bendelac). Therefore, although all the requirements for extrathymic differentiation of lymphocytes within the liver appear to be met, it remains to be established whether it occurs physiologically and what T-cell subsets are involved.

One can only speculate regarding the function of the IHL pool within the liver. It has been proposed that the function of IHL is to maintain a microenvironment favoring homeostasis and tolerance in the absence of pathogens (I. N. Crispe, C. O'Farrelly).[1] The production of foreign antigens by invading pathogens would activate IHL to synthesize cytokines and convert the tolerogenic environment into an immunogenic one. Some experimental results presented during the conference suggested that NK IHL (NK and/or NK T cells) are important for the induction of an intrahepatic immune response and the resultant liver injury. Depletion of NK1.1 cells inhibits delayed type hypersensitivity, cytotoxic lymphocyte (CTL) priming, and liver damage in mice that are experimentally infected with adenovirus (G. Dennert) and decreases interferon gamma and TNF-mediated liver injury induced by polyclonal T-cell activation associated with the lectin ConA (G. Tiegs, Erlangen, Germany).[12] These data suggest that IHLs interact with circulating lymphocytes and may be important players in maintaining the balance between tolerance and the generation of immune responses within the liver.

Alternatively, one can argue that, even in the absence of overt infection, the liver is constantly confronted with pathogens and that the IHLs that are resident in normal liver are participating in a continuous series of intrahepatic immune responses. This could apply to both conventional and nonconventional T cells found within the liver. Supporting this model, most conventional T cells residing in a normal mouse liver appear to have an activated/memory phenotype, whereas a subset of CD8 IHLs residing in normal mouse liver is self-reactive and proliferates when cocultured with syngeneic hepatocytes (P. Bertolino, Sydney, Australia) (manuscript in preparation). Parenchymal cells of the liver could also support activation of CD1-specific nonconventional T cells, because hepatocytes express high levels of CD1 (P. Bertolino, A. Bendelac).

THE LIVER AS A SITE OF LYMPHOCYTE APOPTOSIS

A theme that emerged repeatedly during this meeting was that apoptosis of activated T cells is preferentially detected in the liver. This appears to be the case in a number of different experimental models. Injection of class I–restricted TCR Tg mice with specific peptide or anti-CD3 is followed by a dramatic increase in the number of apoptotic T cells within the liver (I. N. Crispe).[2] These events seem to require an LFA-1/ICAM-1 interaction, and involve CD8 T cells but not CD4 T cells, which preferentially home instead to the lamina propria of the intestine (I. N. Crispe). Similarly, livers from patients who are chronically infected with hepatitis C show a dramatic increase in the resident IHL pool, most of which are apoptotic (S. Abrignani).[3] Apoptosis of self-reactive CD8 T cells was also detected in the liver after hepatic transplantation (S. Qian, Pittsburgh, PA)[13] and in transgenic mice injected with self-reactive naive CD8 cells (P. Bertolino)[14] or with CTL clones specific for a transgenic antigen expressed by hepatocytes (F. Chisari, La Jolla, CA).[15]

Two main hypotheses were proposed to explain why a large proportion of the T cells within the liver appear to be undergoing apoptosis. In the first, the so-called "graveyard hypothesis," the apoptotic T cells that are found in the liver have been activated in the periphery and migrate in a nonspecific fashion to the liver. There, they die either because they are already programmed to do so, or because they are trapped by a non–antigen-specific mechanism and receive an apoptotic signal from liver cells (I. N. Crispe).[16] In the second model, cells undergoing apoptosis have been activated within the liver itself, possibly by hepatocytes functioning as antigen-presenting cells. Direct antigen presentation by hepatocytes, which may be permitted by the fenestrated sinusoidal endothelium of the liver, has been shown in 2 different models (J. Harty, Iowa City, IA; P. Bertolino).[14,17] Activation by hepatocytes that do not express MHC class II molecules would explain why retention and apoptosis of lymphocytes within the liver are restricted to CD8 T cells.

THE TOLEROGENIC ABILITY OF THE LIVER

The unique ability of allogeneic liver grafts to be accepted without immunosuppressive drugs was one of the main topics of the conference. Although tolerance is achieved only between some rat strains, any allo-MHC combination is compatible in mice (S. Qian).[18] Moreover, acceptance of the liver graft induces dominant-specific tolerance to transplants of other organs that would otherwise be rejected.[19] Peripheral tolerance to liver alloantigens was also observed in a double transgenic mouse model in which CD8 T cells expressing a transgenic TCR specific for the allo-MHC class I molecule, H-2 K^b, recognized H-2 K^b expressed in hepatocytes (P. Bertolino).[14] In both models, tolerization is an active process involving activation, proliferation, the generation of CTLs, and apoptosis (S. Qian; P. Bertolino). In the transplantation model, it was clearly shown that tolerance is not caused by soluble class I MHC molecules released by the grafted liver. Allogeneic grafts were accepted even if they were derived from MHC class I–deficient mice or mice matched for MHC class I but differing in class II MHC (S. Qian).[20] Both models suggest that tolerance is achieved by peripheral deletion of self-reactive T cells. It is possible that only T cells bearing a TCR with high avidity for allo-MHC molecules are deleted, paring lower avidity T cells. This would explain why T cells remaining in the periphery or the liver after transplantation are unable to reject the transplant *in vivo* but are functional in *in vitro* assays (S. Qian).[21]

The antigen-presenting cells that are responsible for inducing the peripheral deletion of lymphocytes in this situation are unknown. Microchimerism of donor leukocytes, in particular dendritic cells (DCs), in the lymphoid tissues of the host is often (but not always) associated with liver graft acceptance (A. Thomson, Pittsburgh, PA), suggesting that liver DCs may be involved in induction of tolerance.[22] However, injection of Flt-3 L, which stimulates maturation and increases the numbers of both myeloid and lymphoid-related DCs, leads to rejection of grafts that would otherwise be accepted (A. Thomson).[23] Rejection was costimulation dependent, because graft survival was prolonged if Flt3-L–treated recipients were injected with CTLA-Ig to block the CD28 costimulatory pathway. These results suggest that liver graft acceptance is induced by immature, liver-specific, costimulatory-deficient DCs (A. Thomson).[24]

Some results presented during the conference indicated that CD8 T cells circulating in the blood can also be directly activated by hepatocytes (P. Bertolino, J. Harty, F. Chisari),[14,17,25] implying that the fenestrated endothelium of the liver is permeable to activated as well as naive T cells. Primary T-cell activation by hepatocytes *in vitro* and *in vivo* was found to be abortive and to lead to premature T-cell death and specific tolerance (P. Bertolino).[14,26] These activated T cells may die by "neglect," independently of Fas and TNF receptor, because of the failure of hepatocytes to provide CD28 costimulation. In agreement with this hypothesis, the addition of monoclonal anti-CD28 antibodies or exogenous IL-2 prevented cells from dying in culture (P. Bertolino).[27] Similarly, in a model involving allo-CTL, it was shown that hepatocytes as well as nonparenchymal liver cells are strong inducers of activated CD8 T-cell apoptosis, which occurred during the 4 hours required for a CTL assay (S. Qian). Apoptosis was non–MHC-restricted, independent of members of the TNF receptor family and perforin, but could be inhibited by monodansylcadaverine, a competitor for tissue transglutaminase. Overall, these results suggest that hepatocytes can induce apoptosis of activated T cells by either antigen-specific or -nonspecific mechanisms and that they may be involved in establishing tolerance in the CD8 T-cell compartment after liver transplantation.

INTRAHEPATIC IMMUNE RESPONSES IN BACTERIAL AND PARASITIC INFECTIONS OF THE LIVER

CD4 and CD8 T cells play important roles in the pathology that results from infection within the liver, as well as in the generation of protective immune responses including long-lived memory T cells. However, the nature of these responses varies considerably depending on the specific pathogen. For example, immunization with an attenuated sporozoite can protect mice from experimental plasmodium infection, and this protection is mediated primarily by CD8 cytotoxic lymphocytes that persist in the liver for up to 4 months as a memory T-cell population (U. Krzych, Washington, DC).[28] In this model of human malaria, CD4 T cells, although necessary for the generation of cytotoxic lymphocytes, are not maintained as a long-lived memory T-cell population. CD8 cytotoxic T cells are also potent effectors of adaptive immunity to *Listeria monocytogenes*, but different mechanisms appear to be operative in the liver versus the spleen for controlling growth of this bacterial pathogen (J. Harty). In part, this may be related to the dominant type of antigen-presenting cell that is infected, hepatocytes versus macrophages. In contrast, in experimental shistosomiasis, granuloma formation is mediated by CD4 T cells and, as a key factor in the severity of disease, appears to be regulated by the balance of Th1- versus Th2-type cytokines (M. Stadecker, Boston, MA).[29]

As might be expected, the ability of the host to generate a protective response to a pathogen invading the liver is dependent on both the nature of the antigen and the antigen-presenting cell involved. Using recombinant *Listeria monocytogenes* that express an identical $CD8^+$ T-cell epitope in either a secreted or nonsecreted form, it was shown that only the secreted form induced a protective immunity (J. Harty).[30] The inability of the nonsecreted form to generate protective immunity suggests that hepatocytes are not able to kill the invading intracellular pathogen and correctly process and present peptides from nonsecreted bacterial antigens via the exogenous class I presentation pathway, which is neces-

sary for the generation of protective immunity. Overall, the presentations concerning intrahepatic bacterial and parasitic infections emphasized the complexity of the liver with regards to the manner in which different immune responses are induced by different pathogens.

VIRAL INFECTIONS OF THE LIVER

Some of the most important persistent viral infections occur within the liver. Despite this, the interplay between hepatitis viruses and the immune system is incompletely characterized, and the mechanisms of viral persistence remain poorly defined. However, transgenic mouse models of hepatitis B virus (HBV) infection have yielded provocative hints at what could be happening in acute and chronic HBV infections in humans (F. Chisari). Evidence reviewed during the conference suggests that the early production of interferon gamma by non-CD3 cells (possibly NK cells) may be an important host response that plays a role in controlling and/or eliminating the virus during the early, acute phase of the infection. T cells, both through cytotoxic activity and the secretion of T-cell–derived/induced cytokines, come into play later in the infection to aid in completely eliminating the virus and virus-infected hepatocytes.[31] NK cells and NK T cells have also been shown to play an important role in mediating liver injury in a mouse model of hepatitis by using infection with a type 5 adenovirus (G. Dennert).[4] These cells are necessary for the development of CTLs and for the production of a Th1 cytokine profile.

In transgenic mice expressing HBV proteins, chronic CTL-mediated liver injury has been found to lead with a high frequency to the development of hepatocellular carcinoma (F. Chisari). Thus, in this mouse model, the same T-cell response that can eliminate HBV from the liver when it is sufficiently robust can be procarcinogenic, triggering a chronic necroinflammatory process that leads to cancer when it is unable to effectively eliminate the virus. Such a mechanism may explain, at least in part, the development of liver cancer in patients with chronic hepatitis C, as well as hepatitis B. Thus, the strength of the T-cell response may determine whether the virus infection is eliminated during the acute infection, or allowed to persist within a background of smouldering inflammation that potentially sets the stage for hepatocarcinogenesis. Because many of the cytokines that are involved in promoting the inflammatory response and in limiting virus replication within the liver also contribute to the regeneration of hepatocytes (A. M. Diehl), there appears to be a delicate balance between when an immune response is beneficial and when it is harmful and potentially procarcinogenic.

The roles played by different lymphoid cell populations in both protection against HCV infection and in the production of the pathology of chronic hepatitis C, require further study. Both virus-specific CD4 T cells and CD8 CTLs are present in the liver and peripheral blood of individuals who are chronically infected with HCV (M. Koziel, Boston, MA). These T cells appear to recognize multiple epitopes, with no single immunodominant epitope yet identified.[32] In fact, different epitopes appear to be recognized by T cells that are present in the liver, compared with those that are present in the peripheral blood. To some extent, this may reflect the infection of tissue compartments with different HCV quasispecies, or it could reflect the death of peripherally activated T cells within the liver, because there is little evidence of ongoing clonal expansion within the pool of IHL (S. Abrignani). These observations recapitulate recent observations in the mouse model (I. N. Crispe), as described previously.

CTLs are likely to play a critical role in limiting HCV replication, but they are also believed to play a primary role in the tissue damage associated with chronic infection. In this regard, HCV infection resembles the situation in chronic hepatitis B. However, in immunocompetent persons infected with HBV, the cellular immune system is almost always able to limit virus replication to the point where it is no longer detectable by usual techniques; this is usually not the case in HCV-infected persons. NK cells and/or γδ TCR T cells may also contribute to the liver pathology that develops in chronically infected individuals (S. Abrignani).[3] When compared with peripheral blood lymphocytes, the resident IHL populations in individuals with chronic hepatitis C show an increased number of NK cells, γδ TCR T cells, and Vα24 T cells (S. Abrignani). Additionally, a high percentage of liver biopsy specimens from patients with chronic hepatitis C contain γδ TCR T cells that can be expanded *in vitro* by the addition of cytokines, and these T cells exhibit non–MHC-restricted cytotoxic activity against fresh primary hepatocytes (G. Klimpel, Galveston, TX).

The origin and activation status of the increased numbers of IHLs that are present in individuals with chronic hepatitis C are important questions. An intriguing thought is that HCV has in some way subverted the normal biology of the resident IHL pool in such a way as to escape elimination. Peptide-specific CTLs have been directly identified in the peripheral blood of HCV-infected individuals by labeling with MHC-peptide complexed tetramers, followed by flow cytometry (X. He, Palo Alto, CA). This new technology allows for direct quantitation of HCV-specific T cells in HCV-infected individuals and should provide new exciting opportunities for furthering our understanding of the immune response to HCV and immunopathogenesis of hepatitis C.[33]

SUMMARY

In closing the conference, participants noted general recognition of the unique nature of the intrahepatic immune response. During the meeting, there was a growing realization that investigators with interests in this field would benefit from a multidisciplinary view that takes into account the unique architecture, blood flow, and cellular composition that distinguish the liver from other organs. It is likely that the tolerogenic environment of the liver that contributes to the normal homeostasis of the liver may contribute also to the propensity with which it becomes the site of persistent viral, bacterial, or protozoan infections. A greater understanding of these processes is likely to offer novel strategies for immunotherapy and the elimination of these invading pathogens or at the least an amelioration of the pathogenic consequences of the inflammation they engender.

REFERENCES

1. O'Farrelly C, Crispe IN. Prometheus through the looking glass: reflections on the hepatic immune system. Immunol Today 1999;20:394-398.
2. Huang L, Soldevila G, Leeker M, Flavell R, Crispe IN. The liver eliminates T cells undergoing antigen-triggered apoptosis in vivo. Immunity 1994;1:741-763.
3. Nuti S, Rosa D, Valiante NM, Saletti G, Caratozzolo M, Dellabona P, Barnaba V, et al. Dynamics of intra-hepatic lymphocytes in chronic hepatitis C: enrichment for Valpha24$^+$ T cells and rapid elimination of effector cells by apoptosis. Eur J Immunol 1998;28:3448-3455.
4. Liu ZX, Govindarajan S, Okamoto S, Dennert G. Fas- and tumor necrosis

factor receptor-1 dependent but not perforin-dependent pathways cause injury in livers infected with an adenovirus construct in mice. HEPATOLOGY 2000;31:665-673.
5. Watanabe H, Miyaji C, Kawashi Y, Liai T, Ohtsuka K, Iwanage T, Takahashi-Iwanaga H, Abo T. Relationships between intermediate TCR cells and NK1.1$^+$ T cells in various immune organs. Nk1.1$^+$ T cells are present within a population of intermediate TCR cells. J Immunol 1995;155:2972-2983.
6. Doherty DG, Norris S, Madrigal-Estebas L, McEntee G, Traynor O, Hegarty JE, O'Farelly C. The human liver contains multiple populations of NK cells, T cells, and CD3$^+$ CD56$^+$ natural T cells with distinct cytotoxic activities and Th1, Th2 and Th0 cytokine secretion patterns. J Immunol 1999;15:2314-2321.
7. Kawano T, Cui J, Koezuka Y, Toura I, Kaeko Y, Motoki K, Ueno H, et al. CD1d-restricted and TCR mediated activation of Valpha14 NKT cells by glycosylceramides. Science 1997;278:1626-1629.
8. Kawano T, Tanaka Y, Shimizu E, Kaneko Y, Kamata N, Sato H, Osada H, et al. A novel recognition motif of human NKT antigen receptor for a glycolipid ligand. Int Immunol 1999;11:881-887.
9. Chiu YH, Jayawardena J, Weiss A, Lee D, Park SH, Dautry-Varsat A, Bendelac A. Distinct subsets of CD1d-restricted T cells recognize self-antigens loaded in different cellular compartments. J Exp Med 1999;189:103-110.
10. Crosbie OM, Reynolds M, McEntee G, Traynor O, Hegarty JE, O'Farrelly C. In vitro evidence for the presence of hematopoietic stem cells in the adult human liver. HEPATOLOGY 1999;29:1193-1198.
11. Collins C, Norris S, McEntee G, Traynor O, Bruno L, von Boehmer H, Hegarty J, et al. RAG1, RAG2 and pre-T cell receptor a chain expression by adult human hepatic T cells: evidence for extrathymic T cell maturation. Eur. J Immunol 1996;26:3114-3118.
12. Kunstle G, Hentze H, Germann PG, Tiegs G, Meergans T, Wendel A. Concanavalin A hepatotoxicity in mice: tumor necrosis factor-mediated organ failure independent of caspase-3-like protease activation. HEPATOLOGY 1999;30:1241-1251.
13. Qian S, Lu L, Fu F, Li Y, Li W, Starzl TE, Fung JJ, et al. Apoptosis within spontaneously accepted mouse liver allografts: evidence for deletion of cytotoxic T cells and implications for tolerance induction. J Immunol 1997;158:4654-4661.
14. Bertolino P, Heath WR, Hardy CL, Morahan G, Miller JF. Peripheral deletion of autoreactive CD8$^+$ T cells in transgenic mice expressing H-2Kb in the liver. Eur J Immunol 1995;25:1932-1948.
15. Chisari FV. Hepatitis B virus transgenic mice: models of viral immunobiology and pathogenesis. Curr Top Microbiol Immunol 1996;206:149-173.
16. Crispe IN, Mehal WZ. Strange brew: T cells in the liver. Immunol Today 1996;17:522-525.
17. Harty JT, Bevan MJ. CD8-T cell recognition of macrophages and hepatocytes results in immunity to Lysteria monocytogenes. Infect Immun 1996;64:3632-3633.
18. Qian S, Demetris AJ, Murase N, Rao AS, Fung JJ, Starzl TE. Murine liver allograft transplantation: tolerance and donor cell chimerism. HEPATOLOGY 1994;19:916-924.
19. Kamada N, Davies HfS, Roser B. Reversal of transplantation immunity by liver grafting. Nature 1981;292:840-942.
20. Qian S, Fu F, Li Y, Lu L, Rao AS, Starzl TE, Thomson AW, et al. Impact of donor MHC class I or class II antigen deficiency on first- and second-set rejection of mouse heart or liver allografts. Immunology 1996;88:1168-1163.
21. Dahmen U, Qian S, Rao AS, Demetris AJ, Fu F, Sun H, et al. Split tolerance induced by orthotopic liver transplantation in mice. Transplantation 1994;58:1-8.
22. Thomson A, Lu L. Are dendritic cells the key to liver transplant tolerance? Immunol Today 1999;20:27-32.
23. Qian S, Lu L, Fu F, Li W, Pan F, Steptoe RJ, Chambers FG, et al. Donor pretreatment with Flt-3 ligand augments anti-donor cytotoxic T lymphocyte, natural killer, and lymphocyte-activated killer cell activities within liver allografts and alters the pattern of intragraft apoptotic activity. Transplantation 1998;65:1590-1598.
24. Fu F, Li W, Lu L, Fung JJ, Thomson AW, Qian S. Treatment with CTLA4-Ig inhibits rejection of liver allografts from Flt3-ligand-treated donors. Transplant Proc 1999;31:453-493.
25. Ando K, Guidotti LC, Cerny A, Ishikawa T, Chisari FV. CTL access to tissue antigen is restricted in vivo. J Immunol 1994;153:482-488.
26. Bertolino P, Trescol-Biemont MC, Rabourdin-Combe C. Hepatocytes induce full activation of naive CD8 T cells but fail to promote survival. Eur. J Immunol 1998;28:221-236.
27. Bertolino P, Trescol-Biemont MC, Thomas J, Fazekas de St Groth B, Pihlgren M, Marvel J, Rabourdin-Combe C. Death by neglect as a deletional mechanism of peripheral tolerance. Intern Immunol 1999;8: 101-113.
28. Guebre-Xabier M, Schwenk R, Kzrych U. Memory phenotype CD8($^+$) T cells persist in livers of mice protected against malaria by immunization with attenuated Plasmodium berghei sporozoites. Eur J Immunol 1999;29:3978-3986.
29. Hernandez HJ, Sharpe AH, Stadecker MJ. Experimental murine schistosomiasis in the absence of B7 costimulatory molecules: reversal of elicited T cell cytokine profile and partial inhibition of egg granuloma formation. J Immunol 1999;162:2884-2889.
30. Shen H, Miller JF, Fan X, Kolwyck D, Ahmed R, Harty JT. Compartmentalization of bacterial antigens: differential effects on priming of CD8 T cells and protective immunity. Cell 1998;20:535-545.
31. Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. Science 1999;284:825-829.
32. Wong DK, Dudley DD, Afdhal NH, Dienstag J, Rice CM, Wang L, Houghton M, et al. Liver-derived CTL in hepatitis C virus infection: breadth and specificity of responses in a cohort of persons with chronic infection. J Immunol 1998;160:1479-1488.
33. He XS, Rehermann B, Lopez-Labrador FX, Boisvert J, Cheung R, Mumm J, Wedemeyer H, et al. Quantitative analysis of hepatitis C virus-specific CD8($^+$) T cells in peripheral blood and liver using peptide-MHC tetramers. Proc Natl Acad Sci U S A 1999;96:5692-5697.