Title

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INTRODUCTION

Old and rising stars in the lymphoid liver

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Regardless of the etiology or pathogenesis, chronic liver disease remains a major health issue worldwide and a significant cause of morbidity and mortality particularly when its common outcomes, i.e., liver cirrhosis and primary liver cancer, are observed. As a result, liver diseases cumulatively account for enormous costs, as well represented by health-state utilities and subsequent cost-utility analysis [1]. Table 1 illustrates the available data on disease prevalence, economic costs, and need for liver transplantation in the US. From a clinical standpoint, the majority of conditions remain asymptomatic until advanced stages are established. From a pathogenetic standpoint, all chronic liver diseases manifest one common trait, that is the involvement of the immune system, and over the past decade the role of the liver as a critical immunological center has been established thus overcoming the classical view of this organ as a mere target of the autoimmune or immune-mediated injury.

Indeed, the liver is a unique lymphoid organ being the crossroad at which the majority of antigens enter the organism. The liver is located between the gastrointestinal system and the systemic venous circulation, and every minute approximately one third of the total blood volume passes through the liver delivering over 100 million lymphocytes in 1 day. As a result, the liver must provide an accurate balance between generating tolerance to self as well as to non-pathogenic molecules and microorganisms, and producing an appropriate immune response to pathogens. Furthermore, the mechanisms by which hepatitis viruses cause a liver injury also involve the liver immunological milieu which ultimately constitutes *per se* an important element in the pathogenesis of chronic inflammatory liver diseases, either infectious or autoimmune. The history of the existence of mechanisms capable to induce liver tolerance well illustrates this scenario starting with the first data on the tolerogenic properties of the liver in 1969 when the liver allograft acceptance across an MHC mismatch in the pig was reported [2]. Following these earlier studies, numerous authors have suggested over the decades possible mechanisms underlying hepatic tolerance to intestinally derived antigens or the mechanisms of virus-induced liver injury, yet none of the hypotheses has gained sufficient support for universal acceptance.

As previously mentioned, the lymphoid liver is expected to act in two separate yet closely correlated ways as the first line of defense against invasion by intestinally derived infectious agents or as a site of tolerance. This question becomes particularly relevant in clinical conditions wherein the machinery does not function properly, as in cases of chronic hepatitis virus infections in which an effector immune response is directed unsuccessfully against virally infected hepatocytes, or in liver autoimmunity wherein tolerance to self molecules is inefficient. The present issue of the *Seminars in Immunopathology* will attempt to provide a comprehensive overview of what we currently know on these complex mechanisms. This issue will not discuss the enormous field of the immunology of viral hepatitis; this has been a difficult editorial choice and does not imply a lack of interest in the field. Indeed, new and exciting observations in chronic viral hepatitis C have been

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Table 1 Prevalence, yearly economic cost, and liver transplantation of adult and pediatric liver diseases in the US

	Prevalence [47]	Expenditures (US$ million) [47]	Liver transplantations (% of total) [48]
Adult disease			
Alcoholic liver disease	7.4%	26,400	18%[a]
Non-alcoholic fatty liver disease	20%	–	11%[b]
Hepatitis C	1.8%	1,300	29%[a]
Hepatitis B	4.9%	–	2%
Primary biliary cirrhosis	0.04%	115	9%[c]
Primary sclerosing cholangitis	0.004%	–	–
Autoimmune hepatitis			2%
Hepatocellular carcinoma	0.004%	1,300	13%
Pediatric disease			
Biliary atresia	–	–	3%
Wilson disease	0.003%	–	–

Of note, several data are currently missing due to the lack of solid population-based studies while in some cases multiple etiologies coexist

[a] Patients with mixed etiology (alcohol and HCV) are included in both categories

[b] Cases include also cryptogenic cirrhosis

[c] The percentage refers to cases of cholestatic liver disease (PBC and PSC)

most recently reported in both disease mechanisms [3–6] and therapeutic applications [7, 8] while data on hepatitis B virus also appear promising for novel therapeutic developments [9–11]. On the other hand, we have decided to dedicate the first part of the issue to general issues such as liver microanatomy and architecture. The role of specific cell populations such as the bile duct and the hematopoietic stem cells will be also discussed in dedicated articles to reflect the importance of these cells supported by the most recent data [12–22]. Further, the development of fibrosis is the common outcome of all chronic liver diseases and Dr. Marra and colleagues will illustrate the current knowledge on the role of mononuclear immune cells in determining inflammation and fibrosis, as suggested by the most recent literature [23]. The second part of this issue will be dedicated to specific clinical entities, including biliary atresia, chronic autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis. Finally, a special contribution will be dedicated to the condition that is expected to constitute the major chronic liver disease challenge in the next future, that is, non-alcoholic fatty liver disease and its progressing subtype steatohepatitis. Of note, the pathogenesis of this condition has been subject to a tremendous research effort over the past months [6, 23–39] and we foresee that such interest will increase in the future.

Some outlines from the present days are to provide a snapshot of the several peculiarities of the lymphoid liver. As an example, the liver exhibits unique cytoarchitectural features; there is consignment of proliferating T cells to activation-induced cell death; and there are placating activities in the liver of cell populations such as NKT, Treg, and others. Considering effector activities, there is input from elements of the innate system, neutralizing antibodies, and the well-studied CD4+ helper and CD8+ cytolytic T cell populations that normally provide sturdy responses to intruders ranging from hepatitis viruses to multicellular parasites. However, the necessarily fine immunotuning in the liver may constitute a risk for occurrence of autoreactivity or the occupancy of liver cells by hepatitis B and C viruses and metabolic disturbances such as lipid deposition that alter the normal liver cell structure to provoke profound cytokine and chemokine activation.

The example of primary biliary cirrhosis may well illustrate these concepts as data on the disease pathogenesis are becoming more convincing [40]. The presence of serum autoantibodies and autoreactive T and B cells, in conjunction with the coexistence of other autoimmune diseases, implies an autoimmune pathogenesis for primary biliary cirrhosis while experimental data suggest an important role for the bile duct cell in mediating or facilitating the autoimmune injury. However, the mechanisms for disease onset remain to be determined with putative contributors such as innate immunity or microRNA being studied only recently [41–43].

Another important issue in liver immunology is related to liver transplantation, the only therapeutic option in end-stage liver diseases. Clinical practice has witnessed several advancements in this field, yet legislation and regulations have often failed to keep the pace with the advances in healthcare technology [44]. Current estimates suggest that over 15,000 people in the US await for a liver transplant and this number has been steadily increasing over the past few years while it has been estimated that nearly 4,000 patients are added to the list each month. Conversely, organ donation and transplantation rates recently decreased in the US as 27,958 organ transplant procedures were performed in 2008 (declined by 1.42% from 2007) according to UNOS data. The lymphoid liver is obviously central to the issue of liver transplantation in terms of donor liver and recipient graft tolerance. Two major examples come from the recent observation of occult hepatitis B infection [45]

which has significantly mined the concept of 'healthy' organ donor and the most recent data suggesting that liver immunology is critical to graft tolerance or rejection [46]. Indeed, we hope that the answers to the numerous open questions in liver immunology will be closer following this *Seminars* issue.

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