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Review

Liver auto-immunology: The paradox of autoimmunity in a tolerogenic organ

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ABSTRACT

The study of the liver as a lymphoid organ is a growing field fueled by our better knowledge of the different component of the immune system and how they orchestrate an immune-related response. The liver have highly specialized mechanisms of immune tolerance, mainly because is continuously exposed to microbial and environmental antigens, and dietary components from the gut. Accordingly, the liver contains specialized lymphoid subpopulations acting as antigen-presenting cells. Growing evidences show that the liver is also associated with obesity-associated diseases because of its immune-related capacity to sense metabolic stress induced by nutritional surplus. Finally, the liver produces a pletora of neo-antigens being the primary metabolic organ of the body. Common immune mechanisms play a key pathogenetic role in most of acute and chronic liver diseases and in the rejection of liver allografts. Any perturbations of liver-related immune functions have important clinical implications. This issue of the *Journal of Autoimmunity* is focused on the more recent advances in our knowledge related to the loss of liver tolerance, a paradox for a tolerogenic organ, that leads to overactivation of the innate and adaptive immune response and the development of autoimmune liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. The invited expert review articles capture the underlying immunomolecular mechanisms of the development and progression of autoimmune liver diseases, the novel field of the immune-related "liver-gut" axis influences to the development of liver autoimmunity, the predominant role of genetic factors, and the increasingly effective immuno-therapeutic possibilities.

1. Introduction

The liver performs a very large number of tasks (i.e., protein synthesis and metabolism, including the metabolism of carbohydrates, lipids, amino acids, and vitamins) that also support the function of other organs and impacts almost all physiologic systems. Since large volume of antigen-rich blood is continuously delivered to the liver from the alimentary tract organs, an essential function of the liver is to degradate and to remove toxins, exogenous antigens and infectious agents from the periferal blood circulation. For this reason, the immune system developed specialized mechanisms of immune tolerance able to avoid immune overactivation but also, viceversa, to switch from a tolerant to a responsive state when necessary [1–6]. It is now well accepted that the liver is a mediator of systemic and local innate and adaptive immunity and an important site of immune regulation (Fig. 1).

The first evidence of the uniqueness of the liver in terms of immune system control has occurred with the beginning of the transplant era in the early sixties, when Starzl performed the first human liver transplant [7]. Transplant surgeons noticed that allogeneic liver grafts were more tolerant than other allografts such as kidney, skin, and pancreas, thus suggesting that the liver is biased towards tolerance rather than an immune-reactive state. Few years later, two seminal papers showed that animals tolerated more antigens administered through the portal vein with respect to the systemic circulation [8], and that the liver allografts were not rejected in spite of major histocompatibility complex (MHC) mismatch in animals without immunosuppression [9]. Interestingly, liver transplantation was found to be able to improve the survival of other organ allografts. Based on these early data, it was clear that it would have been possible to develop specific immune therapies both for breaking or for increasing tolerance by acting on

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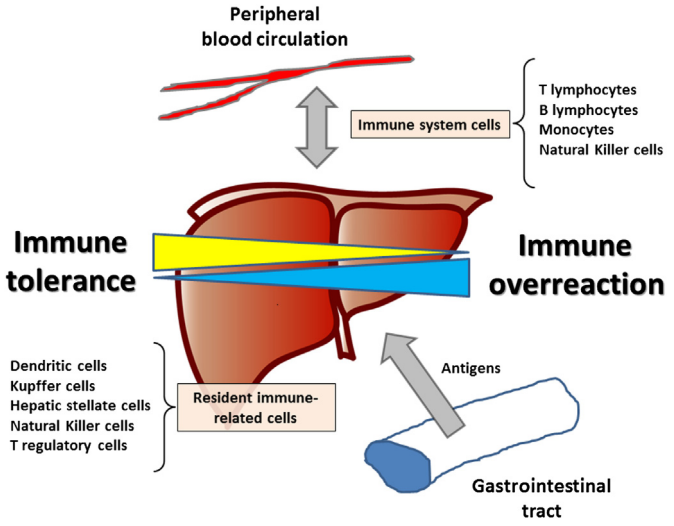

Fig. 1. A schematic representation of the immune function of the liver. The liver received continuously large volume of antigen-rich blood from the gastrointestinal tract. Specialized immune or immune-related cells resident in the liver, can both react with an alert response to potentially hazardous molecules, but can also dampen their responsiveness to further stimuli. There is also a continuous crosstalk between the hepatic immune-related network and the extra-hepatic immune system cells and organs.

the highly specialized liver immune system. However, the underlying reasons for the unique mechanisms of the liver immune system and its predominant tolerant state remained unknown until recently, and further studies are still needed.

Common immune effector mechanisms are known to facilitate liver injury in the course of liver diseases, one of the major causes of morbidity and mortality worldwide. While in acute hepatitis the insult and the repair are generally well compensated [10], in chronic hepatitis an ineffective repair promotes the development of cirrhosis and cancer, which are potentially life threatening for humans and may require organ transplantation [11,12]. For this reason, the development of liver cirrhosis and cancer during chronic liver diseases is the most important problem in our daily clinical practice. Diverse etiologies can cause liver disease, ranging from hepatitis virus infections, such as hepatitis C and B virus [13,14], intoxications to imbalanced diets, including alcohol abuse and steatosis-related pathology [15,16], or autoimmune liver diseases (ALD) such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) [17]. Irrespective of the causes, a better understanding of the underlying immune-related mechanisms is mandatory for the design of new drugs to be used in clinic.

2. Basic mechanisms of immune-mediated liver insult

2.1. Liver anatomy and microanatomy

The liver function to be an immunologic organ is largely achieved thanks to an unique anatomy and microanatomy [18]. First, the liver receives both arterial blood through the hepatic arteries and venous antigen-rich blood from the portal vein, but the venous circulation is more important from an immunological point of view because it delivers to the liver very large volume of antigen-rich blood from the alimentary tract (i.e. stomach, gut, rectum), and the spleen. Second, in addition to the parenchymal cells (hepatocytes and cholangiocytes) the liver contains a plethora of highly specialized non-parenchymal cells that compose five structural systems comprising the vascular system, the hepatic lobule, the hepatic sinusoidal system, the biliary system and the stroma, each of them playing an important role in the homeostasis of the innate and adaptive immune system. In particular, among the non-parenchymal cells there are the liver sinusoidal endothelial cells that lack the basement membrane to allow easy transmission of molecules/antigens from blood to liver parenchyma [19,20], and the hepatic stellate cells that have a intense crosstalk with the immune system cells [21]. Finally, the liver contains a complex repertoires of lymphoid and non-lymphoid cells, key effectors for hepatic immunoregulation and defense [1,5,6].

2.2. Hepatic non-lymphoid cells

The liver contains specialized cells of myeloid lineage that comprise Kupffer cells (KC) [22] and dendritic cells [23,24]. Dendritic cells are the primary antigen-presenting cells of the liver, recently found to be of prevalent myeloid origin [25]. It is to note that also hepatic parenchymal cells such as cholangiocytes can act as antigen presenting cells [26], thus playing a critical role in the hepatic immune function. KC are the largest population of mononuclear phagocytes in the body and already present in the liver during the fetal development. During liver injury and diseases monocytes are known to rapidly differentiate into mature cells that are indistinguishable from genuine KC, independently from the circulating monocytes [27]. The KC strategic position at the luminal side of the liver sinusoidal endothelium is ideal for their prime function, that is surveillance and clearance of the venous portal blood circulation. To maintain the steady state, KC are able to mount opposite responses to exogenous triggers, polarizing to M1 or M2 subphenotypes [28]. They can both react with an alert response to potentially hazardous molecules, but they can also dampen their responsiveness to further stimuli when get in contact to the antigen-rich blood from the gut. Interestingly, KC seems to have a major role in causing loss of tolerance in PBC [26,29].

2.3. Hepatic lymphoid cells

Liver resident lymphocytes are distinct both in function, phenotype, and even perhaps developmentally from their counterparts in the peripheral circulation and in other organs. In particular, they include both conventional (i.e., B cells, CD4+ and CD8+ T cells, natural killer (NK) cells) and non conventional lymphoid cells (i.e., gamma delta TCR+ T cells, NK T cells, CD4-CD8- T cells). Among their liver-specific functions/phenotypes, it has been demonstrated that most of the hepatic T cells are apoptosing peripheral T cells, express the TCR at an intermediate level and the great majority of them coexpress NK cell markers. In addition, the percentage of resting T lymphocytes and B cells are underrepresented in the liver while memory (CD45RB low+) and activated (CD69+) lymphocytes are overrepresented than naive cells (CD62L high). Recent quantitative and functional data showed that the mucosal-associated invariant T (MAIT) cells are a highly specialized T cell population highly adapted to exert their immune functions in the vascular network of the liver [30]. Based on these data, MAIT cells may well play a crucial role in the liver-specific immune mechanisms but further studies are still necessary, in particular in patients with ALD. Regulatory T cell (Treg) populations seem to have an important role in maintaining a beneficial balance in the liver between immuno-tolerance and activation. In particular, solid data showed a role of CD4+CD25+ Treg in the pathogenesis of AIH [31], with clinical implication due to the possible development of therapeutic approaches based on Treg function modulation [32]. On the contrary, in PBC Treg seem