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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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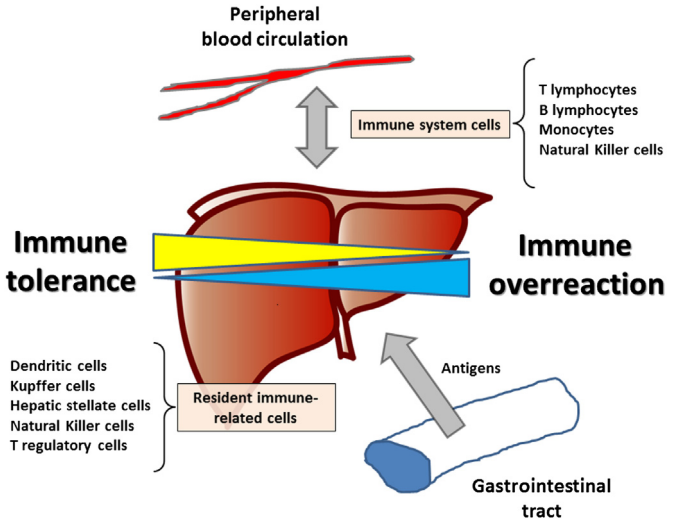

Fig. 1. A schematic representation of the immune function of the liver. The liver received continuously large volume of antigen-rich blood from the gastrointestinal tract. Specialized immune or immune-related cells resident in the liver, can both react with an alert response to potentially hazardous 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

to have a minor role, if any [33,34], while very limited data are available on Treg in PSC.

3. Loss of immune tolerance and development of autoimmune liver diseases

ALD can be classified into two main entities according to the focus of autoimmune injury, i.e. autoaggression against to hepatocyte or to cholangiocyte, and the pattern of inflammation [17,35,36]. Although the ALD are accumulated by the loss of tolerance, their clinical phenotypes and the immunological characteristics differ significantly [37–40]. AIH is a quite uniform condition [40,41], while the autoimmune cholangiopathies comprehends disorders of the intrahepatic biliary ducts such as PBC [26,39,42], and of both the intra- and extra-hepatic one, such as PSC [38], or the immunoglobulin G4-associated cholangitis [43]. There is no doubt on the autoimmune nature of AIH and PBC, while, on the contrary, PSC should be considered an immuno-related other than a classical autoimmune disorder since the lack of some important criteria necessary to define it as autoimmune, i.e. the lack of specific serum autoantibodies [38]. Although the immunoglobulin G4-associated cholangitis is a manifestation of the recently discovered idiopathic IgG4-related disease and its pathogenesis is still largely obscure, its autoimmune nature is suggested by strong responsiveness to steroids [43]. In addition, Beuers and colleagues recently showed that specific B cell responses are pivotal to the pathogenesis of this disorder since the presence of large amount of IgG4+ B cell receptor clones [43,44]. Not rarely, the simultaneous autoaggression against to hepatocytes and to cholangiocytes can cause “overlap syndromes” between PBC and AIH, or PSC and AIH [45].

AIH and PBC have a strong female preponderance, while PSC is more frequent in male. AIH and PSC affect all ages and races, while PBC is rarely seen in children. Immunosuppression is an effective treatment for AIH while PBC and PSC are currently treated with ursodeoxycholic acid, a not toxic an choleretic bile bile acid [37–40]. PBC is characterized by immune cell activation and damage of cholangiocytes of small and medium bile ducts, leading to chronic cholestasis and ultimately hepatic fibrogenesis and liver failure in one third of patients within 10 years from diagnosis [39]. In patients with PSC, both intra- and extra-hepatic bile ducts can be damaged and the disease is characterized by a progressive formation and accumulation of periductular fibrosis, which may resulting in bile duct strictures [38].

3.1. Genetics factors

Different ALD have different and multifactorial pathogenesis, with genetic/epigenetic and environmental factors interplaying to determine disease onset and progression. While our knowledge of the nature and quantification of environmental factors is still very limited [46,47], the genetic architecture of PBC and PSC is now better known thanks to a number of recent genome wide association studies [48–59]. A number of loci have been found to be associated with these autoimmune cholangiopathies, including HLA (consistently the strongest genetic associations) and immune-related non-HLA genes such as IL2, IL12A, IL12RB, STAT4 and CTLA4. Interestingly, it has been reported a shared genetic architecture of PSC and PBC with various other immune-related conditions. However, disease-specific studies are still required to understand the real contribution of these genetic risk factors for the development of each disease and to develop novel therapies. On the contrary to PBC and PSC, genetic associations with HLA and non-HLA genes have been reported in AIH but no large genome wide association studies are still available [40].

3.2. Diagnostic biomarkers

Over the last decade, our approach to diagnose each of the ALD is not significantly changed, consisting first in the exclusion of other causes of liver damage, such as viral, toxic, alcoholic, genetic, metabolic or non-alcoholic fatty liver disease, and then in the evaluation of specific clinical, biochemical, histopathological, and cholangiographic features specific [38–40]. In general, the diagnosis is based on a combination of diagnostic features to obtain a higher sensitivity and specificity.

Serum autoantibodies are the diagnostic hallmarks for PBC and AIH (while no specific autoantibodies were reported in PSC) and seem to allow the identification of subsets of patients with different prognosis [60–64]. Serum hallmarks of PBC patients are the presence of antimitochondrial antibodies and some PBC-specific antinuclear antibodies such as anti-gp210 and anti-sp100 [60,63–65]. Antimitochondrial antibodies are detected in up to 95% of PBC serum samples and their target antigens localized to the inner membrane of the mitochondria; in particular to the E2 subunits of the 2-oxo-acid dehydrogenase multienzyme family, the pyruvate dehydrogenase complex (PDC), the branched-chain 2-oxo acid dehydrogenase complex (BCOADC) and 2-oxoglutarate dehydrogenase complex (OGDC). Two types of AIH can be recognized based on serology: type 1 AIH, characterized by the presence of antinuclear and/or anti-smooth muscle antibodies and type 2 AIH positive for anti-liver kidney microsomal type 1 antibody. While the nuclear and smooth muscle autoantigens are poorly defined, the cytochrome P450IID6, a member of the cytochrome P450 family of hepatic detoxifying enzymes, is the well known antigens for anti-liver kidney microsomal type 1 antibody.

3.3. Liver-gut axis

The human intestinal microflora is considered to be very important in the etiopathogenesis of PSC, mainly because up to 80% of patients with PSC have concomitant inflammatory bowel diseases at some point in their lifetime and about 4% of patients with UC develops PSC [38]. A number of other evidences suggest that intestinal bacteria is a key factor involved in PSC liver inflammation [66]. First, many genes involved in innate immune pathways are increasingly expressed in PSC, and in particular at the late stages of disease. Second, although the strong genetic association with HLA in PSC does not predispose to IBD, a number of non-HLA genetic variants related to mucosal immunity (i.e., macrophage-stimulating-1, IL-2/IL-2 receptor alpha, and caspase-recruitment domain-9) are shared between PSC and IBD [59,67]. Third, the bile of PSC patients often contains enteric bacteria such as *E. coli* and *Candida* [68]. Finally, β-tubulin, the autoantigen of the PSC-associated serum atypical perinuclear antineutrophil cytoplasmic antibodies is known to cross-react with the bacterial cytoskeletal protein FtsZ [69,70]. Thus, a clinically relevant problem that warrants further investigation in the near future is the. Further studies are required to identify the bacterial species that trigger PSC and perinuclear antineutrophil cytoplasmic antibodies and to understand if modulation of gut microbiota might aid in the treatment of this disease.

In PBC, the observations that AMA cross-react with bacterial components, such as *E. coli*, β-galactosidase of *Lactobacillus delbrueckii* proteins [71–73] is considered a key event for its early pathogenesis and suggests an important gut–liver association [66].

3.4. Biliary epithelium

The biliary epithelium is highly heterogeneous, with regard to morphological and phenotypical characteristics [74]. In

particular, it is now well accepted that small and large cholangiocytes have different secretory, apoptotic and proliferative responses. PBC and PSC, the two most common cholangiopathies observed in the biliary epithelium, are characterized by cholangiocytes proliferation/apoptosis, inflammation and fibrosis of different sized bile ducts, in other words by a “biliary epithelitis” [26,75].

The biliary and gut epithelia are contiguous components of the mucosa and have common barrier functions and mechanisms to defend from pathogens. This is of particular interest to understand the pathogenetic mechanisms underlying the development of PSC [38]. For an in-depth discussion of the role of biliary epithelium and a biliary epithelitis in PSC genetics we refer the reader elsewhere [Trivedi et al. 2013]. With regard to the PBC pathogenesis, it is instructive to consider the large number of similarities between this autoimmune cholangiopathy and Sjogren syndrome, an autoimmune disease due to aggression to salivary and lachrymal ducts [76–100]. Indeed, both diseases frequently overlap with each other, with most of PBC patients suffering from sicca and some of them have a classic Sjogren’s syndrome. Both PBC and Sjogren’s syndrome are characterized by inflammation of target epithelium, a condition that can named “autoimmune epithelitis”.

The current proposed immunopathogenesis of PBC and Sjogren’s syndrome suggest, as a triggery event, that environmental factors cause biliary or salivary/lachrimatory epithelial cell apoptosis, thus contributing to tolerance loss to autoantigens possibly not protected by posttranslational modification (PDC-E2), or exposed on the apoptotic blebs (SSA and SSB). It is also known that biliary epithelial salivary/lachrimatory cells concur to the autoimmune process by expressing adhesion molecules, HLA class II, and cytokines. Recent evidences from large genome wide association studies both in PBC and in Sjogren’s syndrome suggest that common inflammatory genes may have a role in these disease [53,101,102]. In the future it will become critical elements to dissect the genetic predispositions for both diseases and in particular the molecular basis of effector mechanisms, also to develop new therapies.

4. Concluding remarks

Evidences supporting the concept that the liver is a lymphoid organ are available since the early sixties, but only in the last few years we started to dissect the underlying mechanisms that makes the liver an unique organ in the human body for its ability to balance between immune tolerance and overreaction. This critical and complex function of the liver is obtained thanks to a peculiar anatomy and microanatomy, unique features of hepatic parenchymal cells and a large number of resident immune and immune-related cells. One of the area which is more benefiting from these advances, it is that related to ALD, liver diseases due to a loss of tolerance. Liver autoimmunity is indeed a great paradox for an organ with peculiar tolerizing properties. Growing amount of evidences are dissecting the complex mechanisms which coordinate immune responses between the liver and gut, and the role of gut bacteria in ALD. As for many other complex diseases, genome wide association studies are providing important information on the ethiopathogenesis of ALD. Of course, the accumulating knowledge from these generic studies needs to be confirmed and explored in the context of functional studies with the ultimate goal of developing novel therapeutic approaches for ALD. There is no doubt that we are witnessing the birth of a new era of clinical opportunities, but the real challenge is now to transfer these “basic” knowledge to the clinical arena with a beneficial impact to our patients.

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