γδ T cells in liver diseases

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Abstract γδ T cells display unique developmental, distributional, and functional patterns and can rapidly respond to various insults and contribute to diverse diseases. Different subtypes of γδ T cells are produced in the thymus prior to their migration to peripheral tissues. γδ T cells are enriched in the liver and exhibit liver-specific features. Accumulating evidence reveals that γδ T cells play important roles in liver infection, non-alcoholic fatty liver disease, autoimmune hepatitis, liver fibrosis and cirrhosis, and liver cancer and regeneration. In this study, we review the properties of hepatic γδ T cells and summarize the roles of γδ T cells in liver diseases. We believe that determining the properties and functions of γδ T cells in liver diseases enhances our understanding of the pathogenesis of liver diseases and is useful for the design of novel γδ T cell-based therapeutic regimens for liver diseases.

Keywords γδT cells; liver infection; non-alcoholic fatty liver disease; autoimmune hepatitis; liver fibrosis and cirrhosis; liver cancer; liver regeneration

Introduction

γδ T cells belong to a unique innate lymphocyte subset. Research on the differentiation, distribution, function, and application of γδ T cells has achieved considerable progress since the discovery of the γδ T-cell lineage approximately 30 years ago. T cells develop from multipotent progenitor CD4−CD8-double-negative (DN) thymocytes in the thymus and undergo four stages (DN1, CD44+CD25−; DN2, CD44+CD25+; DN3, CD44 CD25−; and DN4, CD44 CD25−) [1]. T-cell receptor (TCR) rearrangement begins at the DN2–DN3 stages, and γδ TCRs or preTCRs are expressed at the DN3–DN4 stages [2]. Cell differentiation into αβ or γδ T-cell lineages is determined at the DN3 stage [3]. γδ T cells can produce at least two distinct subsets, namely, interferon (IFN)-γ- and interleukin (IL)-17-producing γδ T cells. The segregation of γδ T-cell functional subsets can be distinguished by cell surface markers. CD27 segregates γδ T cells into IL-17-producing CD27−γδ T cells, and IFN-γ-producing CD27+γδ T cells [4]. CCR6+ γδ T cells exclusively produce IL-17A, whereas NK1.1+ γδ T cells readily produce IFN-γ [5]. Increasing evidence suggests that the functional polarization of γδ T cells is developmentally programmed in the thymus rather than in localized peripheral tissues [6]. Therefore, TCR signals play an essential role, beyond lineage commitment, in the functional polarization of γδ T cells. In contrast to conventional adaptive T cells, which recognize peptide antigens presented by antigen-presenting cells in a MHC-dependent manner, γδ T cells can recognize nonpeptide antigens and stress-induced ligands [7]. Moreover, γδ T cells are preferentially located in peripheral mucosal tissues [8] and play a protective role in pathogen clearance, tumor surveillance, and tissue repair and a deleterious role in autoimmunity, allergy, and carcinogenesis through cytokine secretion and/or cytotoxicity [9]. Thus, γδ T cells contribute not only to immune balance and tissue homeostasis but also to immune disorders and tissue pathogenesis. In fact, the effector functions of γδ T cells are determined by developmental polarization, tissue localization, and environment cues. Growing evidence reveals that γδ T cells in the liver respond to liver-targeted insults and modulate the development of liver diseases [10,11]. As such, this review focuses on the roles of γδ T cells in liver diseases (Fig. 1).

Although the liver is recognized as an important organ in
the defense against blood-borne infections, liver injury can also be triggered by drugs, toxins, pathogen infections, over-eating, and genetic disorders [12]. Moreover, persistent liver damage is likely to induce the progression of mild chronic liver disease to liver fibrosis, liver cirrhosis, liver cancer, and liver failure [13]. The liver displays tissue-specific features that need to be emphasized in this study because prior knowledge of these features enhances the understanding of the induction, development, and end stage of liver disease. First, the liver is a barrier organ that segregates the digestive tract from the rest of the body. It possesses a special blood circulation system, wherein 80% of blood supply from the portal vein is rich in bacterial products, environment toxins, and food-derived antigens that are purified by the liver from the intestines; meanwhile, the remaining blood from the hepatic artery provides nutrients and oxygen [14,15]. Second, the liver is an immune-tolerant organ. Liver tolerance is manifested by immune hyporesponsiveness in the context of allogeneic liver transplants and liver infections and is maintained and modified by diverse intrahepatic cells, including immune cells and non-immune cells [16,17]. Third, the liver is an organ with predominant innate immunity. It is enriched with Kupffer cells, natural killer cells, natural killer T (NKT) cells, and γδ T cells [18–22]. These liver features reflect the close relationship among its anatomical location, immune status, immune components, functions, and liver disease. In this study, we highlight advances in the understanding of the properties and roles of hepatic γδ T cells in liver diseases and discuss the potential of γδ T cells as therapeutic targets in treating liver diseases.

**Hepatic γδ T cells**

γδ T cells constitute approximately 2%–10% of the total T cells in the peripheral blood, whereas hepatic γδ T cells account for 3%–5% of the total liver lymphocytes and 15%–25% of the total number of liver T cells [18]. In terms of phenotype, hepatic γδ T cells exhibit mixed Vγ chains (including Vγ1, Vγ4, and Vγ6 in mice and Vδ1 and Vδ3 in humans) [23]. Hepatic γδ T cells in the murine liver contain a high fraction of Vγ4+ cells with enhanced functional activation; meanwhile, hepatic γδ T cells in the human liver are more mature than their counterparts in peripheral blood [24]. Recently, our group carefully analyzed hepatic γδ T cells [25]. Hepatic γδ T cells are highly localized to the...