Liver Resident Memory T Cells

Subjects: Immunology

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Immunological memory is fundamental to maintain immunity against re-invading pathogens. It is the basis for prolonged protection induced by vaccines and can be mediated by humoral or cellular responses - the latter largely mediated by T cells. Memory T cells belong to different subsets with specialized functions and distributions within the body. They can be broadly separated into circulating memory cells, which pace the entire body through the lymphatics and blood, and tissue-resident memory T (TRM) cells, which are constrained to peripheral tissues. Retained in the tissues where they form, TRM cells provide a frontline defense against reinfection. Here, we review this population of cells with specific attention to the liver, where TRM cells have been found to protect against infections, in particular those by Plasmodium species that cause malaria.

resident memory T cells liver

1. Introduction

The successful containment of infections relies on the speed with which immune responses of sufficient intensity are mounted. Immunological memory enables the long-term maintenance of a small fraction of those cells that responded to and resolved an earlier infection. The number of specific memory T cells generated after an infection, while declining over time, is generally larger than that of naïve T cells of the same specificities [1]. In addition, memory T cells display an enhanced antigen sensitivity, requiring lower levels of antigen for activation [2]. Memory T cells thus respond more rapidly and potently to pathogen invasion, and can exert efficient protection, potentially lifelong, against previously encountered infections. Different subsets of memory $CD8^+$ T cells have been identified on the basis of their migratory properties, e.g., circulatory memory T cells and resident memory T cells (T_{RM} cells). The latter have recently emerged as important mediators of protection in peripheral organs, a common point of entrance of pathogens, by inducing rapid and local responses upon antigen recall [3]. By combining transcriptional and phenotypic features with different approaches to investigate residency, studies have identified T_{RM} cells in various disease models and within several tissue settings, including the liver. Importantly, strategies have been devised to favour the formation of T_{RM} cells through vaccination, achieving promising results, for example, in the case of herpes virus infection in the mucosa of the female genital tract [4] and *Plasmodium* infection of the liver [5][6][7][8][9].

The liver is essential for the maintenance of homeostasis and is central to many metabolic and immunological processes. Hepatic functions are tightly regulated; and disturbances that lead to liver diseases such as microbial infections, chronic inflammation or cancer can result in death. The liver is also the target of certain pathogens, such

as *Plasmodium*, *Leishmania*, or *Listeria*, which infect and develop in this organ during stages of their life cycles. Given the highly protective capacity of memory T cells, and in particular of T_{RM} cells, studying the biology of these cells may aid the development of prophylactic and therapeutic strategies against life-threatening conditions associated with organ damage or infection.

2. Resident Memory T Cells

As they are an essential first line of defense against pathogen invasion in most tissues, T_{RM} cells have become a major focus of T cell research throughout the last decade. They have been identified in virtually all organs in mice [10][11] and humans [12] including lymphoid and non-lymphoid tissues (Table 1). While we will focus on $CD8^+$ T_{RM} cells in this review, T_{RM} cells can derive from both $CD4^+$ and $CD8^+$ T cells.

Identification of cell surface markers that can clearly distinguish T_{RM} cells from other memory T cell subsets in both mouse and human tissues is complicated by the fact that no single marker associated with T_{RM} cells is exclusive to this cell subset. In the following table we try to summarize the expression of the canonical markers used to define $CD8^+$ T_{RM} cells in diverse murine and human organs.

Table 1. Expression of the canonical markers used to define $CD8^+$ T_{RM} cells in diverse murine and human organs.

Organs	Expression of Canonical Markers (CD69, CD103, CD49a and CXCR6)	
	Mice	**Humans**
Intestine, Gut	CD69+ CD103+/− CD49a+ CXCR6+	CD69+ CD103+
Skin	CD69+ CD103+/− CD49a+	CD69+ CD103+/− CD49a+/−

	CXCR6+	
Lungs	CD69+ CD103+ CD49a+ CXCR6+/-	CD69+ CD103+ CD49a+ CXCR6+
Female reproductive tract	CD69+/− CD103+/−	CD69+ CD103+ (transcriptomic profiling is yet to be determined)
Salivary glands	CD69+/− CD103+/− CD49a+	CD69+ CD103+/−
Lymphoid organs **(Spleen, lymph nodes, tonsil)**	CD69+ CD103− CD49a+	CD69+ CD103+/− CD49a-
Liver	CD69+ CD103−	CD69+ CD103+/−

	CD49a+ CXCR6+	CXCR6+
Kidneys	CD69+/− CD103-	CD69+ CD103+/− CD49a+/− CXCR6+/−
Pancreas	CD69+/− CD103+/−	CD69+ CD103+ CD49a+ CXCR6+
Brain	CD69+ CD103+/−	CD69+ CD103+/− CD49a+ CXCR6+/−

3. Liver T_{RM} cell identification

Malaria is a major infectious disease caused by *Plasmodium* parasites. In their vertebrate host, parasites first develop in the liver for a short period of time, where they infect hepatocytes, before being released into the bloodstream to cause blood-stage infection, which leads to disease symptoms. Early evidence supporting the existence of resident memory T cells in the liver came from studies investigating the role of $CD8^+$ T cells against

the liver-stage of *Plasmodium*. These studies identified a long-lasting population of memory $CD8^+$ T cells present in the liver and absent in the spleen of mice vaccinated with radiation-attenuated *Plasmodium* sporozoites (the infectious stage transmitted by the mosquito) [13]. Vaccinated mice were protected against *Plasmodium* sporozoite challenge for more than 6 months [13]. Later reports revealed that a subpopulation of memory $CD8^+$ T cells associated with the liver, but absent from the circulation, expressed high levels of CXCR6, CXCR3, and CD69 [5][14], markers commonly displayed by T_{RM} cells [15].

The presence of bona fide memory cells permanently residing in the liver was confirmed by parabiosis studies in mice systemically infected with LCMV or *Plasmodium* sporozoites [6][11]. Parabiosis requires the surgical union of the flank skin of two animals. This enables the mixing of blood between the parabionts, and thus evaluation of T cell migration from one animal to the other. Unlike circulating cells, which equilibrate between both animals, resident populations remain in the parabiont in which they originally formed. This technique has been extensively used to identify T_{RM} cells in different murine tissues [11]. Although liver T_{RM} cells are in constant contact with circulating blood [6], parabiosis studies have confirmed that these cells, counterintuitively, do not recirculate and can only be found in the livers of the immunized parabiont partner [6][11].

Liver T_{RM} cells were found to express a similar phenotypic and transcriptional signature to that of T_{RM} cells previously identified in the lung, skin, and gut [6][16]. Maintenance of liver T_{RM} cells in mice relies on the expression of the transcription factor Hobit, and on basal levels of expression of Blimp1 [17]. These T_{RM} cell signatures have been found in T cells from grafted or isolated human tissues, enabling the unequivocal identification of T_{RM} cells in several human organs [18], including the liver [19][20]. As mentioned earlier, contrary to liver T_{RM} cells in mice which express high levels of Hobit and low to intermediate levels of Blimp1 [17], human liver T_{RM} cells are $Hobit^{low}$ $Blimp1^{high}$ [19]. In a recent publication, a small proportion of donor cells were found in HLA-mismatched liver and allografts 11 years after transplant, demonstrating the resident nature and remarkable longevity of these cells [21].

4. Liver T_{RM} cell location

The liver is the recipient of both arterial and venous blood. The portal vein delivers large volumes of blood from the gastrointestinal tract and spleen to the liver. Once there, the blood flows through narrow vascular capillaries known as hepatic sinusoids, which reduce the flow rate and allow resident cells to interact with a vast variety of antigens and circulating cells [22]. The hepatic sinusoids are lined with liver sinusoidal endothelial cells that form a fenestrated thin layer that separates hepatocytes from circulating cells. These fenestrae grant lymphocytes in the blood direct access to the surface of hepatocytes for antigen recognition and effector function [23][24]. In contrast to T_{RM} cells in most tissues, which are anatomically separated from the circulation, liver T_{RM} cells are present within the sinusoids and are constantly exposed to the blood stream but are able to access antigen on tissue stroma through the fenestrated endothelium [6]. Intravital images shows that liver T_{RM} cells, which display an ameboid shape, are uniquely located in the vasculature where they patrol the hepatic sinusoids at migration speeds more rapid than seen for skin T_{RM} cells (Figure 1) [6][11][17].

Figure 1. The liver is a unique niche for tissue resident memory cells. The portal vein delivers antigen-rich blood from the gastrointestinal tract and spleen to the liver. This blood flows through the liver hepatic sinusoids lined with a thin layer of fenestrated liver sinusoidal endothelial cell (LSEC). Liver T_{RM} cells are localized within the hepatic sinusoids, where they remain long-term and do not recirculate despite direct connection to the circulatory system and constant exposure to the blood. The expression of ICAM-1 and CXCL16 by LSEC can promote the retention of lymphocytes, through interactions with LFA-1 and CXCR6, respectively. Murine and human T_{RM} cells in the liver express CD69, CXCR6, CXCR3 and high levels of LFA-1. Of note, human but not murine T_{RM} cells express CD103. It has been suggested that this difference is associated with a broad versus a restricted expression of E-cadherin by human and murine hepatocytes, respectively. Intrahepatic lymphocytes including circulating and resident memory cells can access the surface of hepatocytes through LSEC fenestrae and exert effector functions. Using cytoplasmic protrusions, lymphocytes probe hepatocytes for the presence of antigen and can release factors such as GzmB and IFN-γ to promote hepatocyte killing. In murine studies, liver T_{RM} cells can be generated through different vaccination strategies to confer protection against *Plasmodium* parasites and in humans they have been associated with disease control against HBV and HCV.

5. Liver T_{RM} cell immune responses to infection

Murine studies have shown that liver T_{RM} cells can confer efficient protection against liver-stage *Plasmodium* infection [6][9]. These studies have also demonstrated that substantial numbers of liver T_{RM} cells are associated with higher levels of immunity to malaria, and depletion of these cells ablates protection [6][9]. Based on these results, several complex vaccinations strategies, aimed at trapping activated $CD8^+$ T cells in the liver, have now successfully induced the formation of liver T_{RM} cells in mice [6][7][8][9]. One vaccination strategy, prime-and-trap, is a single injection of a 3-component vaccine designed to prime *Plasmodium*-specific $CD8^+$ T cells in the

spleen and recruit them to the liver to form T_{RM} cells via locally expressed antigen recognition and adjuvant-induced inflammation [6][9]. Another strategy, termed prime and target requires the administration of two components injected two weeks apart and uses a modified adenovirus for priming and either nanoparticles or a modified viral vector to target cells to the liver [7]. More recently, we have also used a glycoprotein-peptide vaccination strategy that utilizes NKT cell help to induce the formation of liver T_{RM} cells [8]. In mice, vaccine-induced T_{RM} cells patrol the liver sinusoids, form aggregates around infected hepatocytes and, based on expression of molecules such as GzmB, IFN-γ and TNF-α (Figure 1) [6][7], potentially exert infection control through direct lysis and/or cytokine-mediated mechanisms. Moreover, vaccination studies with attenuated *Plasmodium* sporozoites in non-human primates have found high frequencies of intrahepatic memory $CD8^+$ T cells in protected subjects [25].

Importantly, in humans, liver T_{RM} cells have been associated with disease control. For example, recent studies have investigated paired blood and liver samples from patients with chronic hepatitis B and hepatitis C virus infection and healthy volunteers to determine the role of liver T_{RM} cells during viral infections [19][20]. Researchers found that human T_{RM} cells in the liver express high levels of IL-2 and accumulate in larger numbers in the livers of infected patients compared to healthy patients. These studies also determined higher expression of GzmB and IFN-γ in HBV infected patients. Importantly, an inverse correlation between liver T_{RM} frequencies and viral titers was observed, indicating that high numbers of specific liver T_{RM} cells were associated with viral control [19]. However, accumulation of intrahepatic $CD8^+$ $CD103^+$ $perforin^+$ T cells has been observed in cases of autoimmune hepatitis, particularly in indeterminate pediatric acute liver failure [26]. These findings suggest that liver T_{RM} cells could also have a pathogenic function.

6. Conclusions

T_{RM} cells are pivotal mediators of protective immune responses within tissues and have been identified in nearly all organs, including lymphoid, non-lymphoid and barrier tissues. They are loaded with effector molecules, including GzmB, perforin, IFN-γ, and TNF, and likely exert their function by the direct killing of targets, or by recruiting other immune cells. Several infection models have correlated the presence of T_{RM} cells with pathogen and tumour control in tissues. Notably, in the liver, $CD8^+$ T_{RM} cells can mediate efficient control of liver-stage *Plasmodium* parasites, and likely, HBV and HCV infections. For this reason, T_{RM} cells appear of particular interest in the course of vaccine development, especially for liver T_{RM} cells for malaria vaccines. Further research unveiling the mechanisms for the formation and maintenance of T_{RM} cells will facilitate the design of next generation T_{RM}-based vaccines that realize the protective potential of these cells for unprecedented immunity against infections.

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