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Review article

Tissue-resident memory $CD8^+$ T cells: master deciphers of the hepatic environment

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Abstract

Tissue-resident memory $CD8^+$ T ($CD8^+$ T_{RM}) cells are localized within peripheral tissues, such as the liver, poised to provide effective immunosurveillance, as well as rapid and enhanced effector functions upon stimulation. Here we review how hepatic $CD8^+$ T_{RM} cells decipher a myriad of environmental signals, ranging from cellular and soluble factors to direct interactions with the underlying stroma and structural tissue niche, which dictate their derivation, retention and function. We discuss insights from both mouse and human studies that have contributed to our understanding of how $CD8^+$ T_{RM} cells can, depending on the context, provide targeted antigen-specific antiviral and antitumour immune responses and elicit antigen-independent tissue-damaging responses that contribute to liver pathology. Specifically, we discuss how the $CD8^+$ T_{RM} cell functional response is shaped by multiple factors and how such environmental cues tip the balance between these dual 'Jekyll and Hyde' response modes. Finally, we examine strategies to better identify and characterize hepatic $CD8^+$ T_{RM} cells and how the enhanced functionality of $CD8^+$ T_{RM} cells can be harnessed therapeutically in the context of hepatocellular carcinoma.

Sections

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Key points

- A population of long-lived hepatic CD8$^+$ T cells interpret, integrates and responds to various environmental signals, ranging from metabolic and soluble mediators to direct cell–cell or cell–extracellular matrix interactions.

- Localized tissue-resident memory CD8$^+$ T (CD8$^+$ T$_{RM}$) cells can elicit both immunoprotective and immunopathogenic effector functions within the liver.

- The functional response mode of hepatic CD8$^+$ T$_{RM}$ cells is shaped and/or regulated by context-specific cues.

- The enhanced retention within tumours and rapid effector function of CD8$^+$ T$_{RM}$ cells could be harnessed for therapeutic intervention, such as chimeric antigen receptor T cell therapy for hepatocellular carcinoma.

Introduction

CD8$^+$ T cells are an essential component of the adaptive immune response, guarding against viruses, intracellular bacteria and other threats to health. Although many CD8$^+$ T cell populations continually migrate throughout the host, it is increasingly difficult to ignore the fact that most memory T cells durably reside in peripheral tissues[1,2]. Tissue-resident memory T (T$_{RM}$) cells survey tissue compartments with a limited ability to recirculate, remaining poised to respond to antigenic encounters, having crucial roles in accelerated protection against recrudescent, latent or re-encountered infections and malignancy[3–5]. The ability of memory T cells to survey peripheral tissues, monitoring local perturbations in homeostasis and to respond to insults requires cell-to-cell, contact-dependent antigen recognition. Thus, the precise location and interdependence of T cells on cues from their microenvironment are essential for their function.

Although T$_{RM}$ cells occupying specific organs have unique qualities, they share a core molecular signature and the ability to survive long term in their preferred niche, deciphering, integrating and adapting to a myriad of distinct local cues[2,6,7]. As potent immune sentinels, T$_{RM}$ cells take advantage of their tissue compartmentalization to mount highly specialized, local, rapid and effective responses by secreting cytokines and chemokines in deployment-ready mode[8]. Although T$_{RM}$ cells are most often thought to promote favourable antiviral and antitumour immune responses, there is a growing appreciation that dysregulated T$_{RM}$ cell responses can be detrimental, contributing to inflammation and/or tissue damage when mistargeted[9]. Hepatic CD8$^+$ T$_{RM}$ cells are no different.

Seminal studies have begun to reveal two co-existent but seemingly opposed T$_{RM}$ cell response modes, which are dependent on environmental cues. Here we discuss this ‘Jekyll and Hyde’ concept (Box 1), focusing on CD8$^+$ T$_{RM}$ cell phenotype and function. We define the characteristic features of the immunoprotective ‘favourable’ (Jekyll) response mode and the immunopathogenic ‘detrimental’ (Hyde) response mode (Fig. 1 and highlighted in Table 1), calling to attention cell-intrinsic and cell-extrinsic signals that tip the balance between response modes, drawing on studies in mice and humans.

Protective (Jekyll) and pathogenic (Hyde) hepatic CD8$^+$ T$_{RM}$ cells

Functional CD8$^+$ T cell responses are crucial for effective viral clearance in the liver[10,11]. In particular, hepatic CD8$^+$ T$_{RM}$ cells are essential for mediating robust antiviral immunity[12–14]. As a result, eliciting strong functional responses within these cells is desirable when designing therapeutic vaccines to prevent the progression of, or potentially cure, chronic hepatitis B virus (HBV) infection[15,16]. Beyond antiviral defence, hepatic CD8$^+$ T$_{RM}$ cells patrol the sinusoids, providing effective immune surveillance against liver-stage *Plasmodium* spp. infection[17–20], with the frequency of hepatic CD8$^+$ T$_{RM}$ representing a key correlate of protection in vaccination strategies against *Plasmodium* spp. Moreover, hepatic CD8$^+$ T$_{RM}$ cells have a critical role in tumour surveillance, with several studies suggesting that a predominance of CD8$^+$ tumour-infiltrating lymphocytes with a resident-cell phenotype (CD69-expressing ±CD103) corresponds with better patient outcomes, including improved overall survival[21–24] in human hepatocellular carcinoma (HCC). In addition, one study has also attributed antifibrogenic properties to hepatic CD8$^+$ T$_{RM}$ cells in a mouse model of metabolic dysfunction-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis) resolution, showing that through the FAS–FAS ligand pathway, CD8$^+$ T$_{RM}$ cells are capable of eliminating the activated myofibroblasts mediating the deposition of extracellular matrix (ECM) proteins[25].

Although the protective role of CD8$^+$ T cells is widely recognized, the discovery that certain CD8$^+$ T cells can reside long term in the liver[20,26] greatly accelerated research into the characterization of hepatic CD8$^+$ T$_{RM}$ cells and has deepened our understanding of their contribution to the pathogenesis of various liver diseases. Emerging evidence in humans indicates that antigen-independent mechanisms, commonly referred to as bystander activation of hepatic CD8$^+$ T$_{RM}$ cells, can contribute to liver tissue damage during viral infections such as hepatitis A, hepatitis B, hepatitis C and hepatitis D[27–31]. This process, driven by inflammatory signals such as heightened local IL-15 signalling, is thought to support viral clearance[32,33]. However, in cases in which viral clearance fails, persistent bystander activation can trigger and sustain molecular cascades that drive tissue remodelling, ultimately contributing to the development of chronic liver diseases, including cirrhosis and HCC[34,35]. The latter represents an example of the Jekyll and Hyde concept in individuals living with chronic hepatitis B (CHB), in which HBV-specific CD8$^+$ T cells in the liver undergo functional adaptation to minimize tissue damage and contribute to viral control[10,12,36]; however, inflammation-driven, bystander non-HBV-specific CD8$^+$ T$_{RM}$ cells can contribute to liver pathology[31]. Remarkably, the increased hepatic accumulation of CD8$^+$ T$_{RM}$ cells driven by the highly inflammatory liver environment has also been observed in the context of non-viral chronic liver diseases such as MASH[37,38], autoimmune hepatitis[39], primary sclerosing cholangitis (PSC)[40], cirrhosis[41] and idiosyncratic drug-induced liver injury[42], contributing to liver pathology. In mice models of MASH-HCC, pathogenic PD1$^+$CD8$^+$ T$_{RM}$ cells could even promote the onset of HCC within an inflammatory liver microenvironment – an effect that can be further exacerbated by immune checkpoint blockade therapy[43]. Whether the increased emergence of pathogenic T$_{RM}$ cells in non-viral chronic liver diseases results from heightened inflammation or antigen-driven processes is currently unclear, as no specific immunogenic autoantigens driving the clonal expansion of CD8$^+$ T cells have been characterized in these diseases[38].

Together, these studies highlight the critical need to identify the environmental signals that dictate the emergence of either protective (Jekyll) or pathogenic (Hyde) hepatic CD8$^+$ T$_{RM}$ responses during liver inflammation and disease[43–45] (Fig. 1).

Deciphering a myriad of environmental cues in the liver

The unique structural and cellular architecture of the liver

One reason why CD8$^+$ T$_{RM}$ cells are exposed to a myriad of environmental cues stems from the unique anatomy of the liver. The liver consists of repeating anatomical hexagonal units termed lobules, comprising radiating rows of hepatocytes (Fig. 2). The blood flows through an extensive network of sinusoidal vessels from two distinct sources: the portal vein, carrying oxygen-poor, nutrient-rich blood from the gastrointestinal tract and oxygenated blood from the hepatic artery[46,47]. Portal triads – consisting of branches of the hepatic artery and portal vein, bile ducts and the occasional lymphatic vessel – surround each lobule (Fig. 2). Blood enters the periphery of each lobule, flowing towards a single central vein, whereas bile flows outwards from the lobule centre, draining into the portal bile duct. This architecture creates three distinct zones that can substantially affect both resident and liver-infiltrating cells: the periportal zone near the portal triad (zone 1), the pericentral zone surrounding the central vein (zone 3), and a mid-lobular region critical for homeostatic maintenance of liver mass and regeneration (zone 2)[48,49] (Fig. 2). The unique anatomy of the liver also accommodates several highly specialized cell types: Kupffer cells (liver-resident macrophages)[50], hepatic stellate cells (HSCs) serving as specialized pericytes[51] and liver sinusoidal endothelial cells (LSECs), which are fenestrated and lack both tight junctions and a continuous basement membrane[52]. This structural feature enables direct hepatocyte–leukocyte interactions. To survey antigens presented by hepatocytes through fenestrated LSECs, patrolling T cells have to 'squeeze' through the vasculature because sinusoidal blood vessels are approximately 6–15 μM in diameter and CD8$^+$ T cells range from 5 μM to 10 μM (depending on activation status)[47,53,54].

In doing so, CD8$^+$ T cells constantly sense and transmit instructions from the environment by integrating signals from direct cell–cell interactions, assessing nutrient availability, responding to mechanical and physical stress and translating biochemical alterations[55–57] (Fig. 3).

As a result, from the hepatic architecture and the complex interplay between various specialized cell types in the liver microenvironment, hepatic T$_{RM}$ cells use a range of receptor–ligand interactions and transcriptional regulators to dictate their retention, location and functional adaptation within the liver. One of the key defining features of CD8$^+$ T$_{RM}$ cells, distinguishing them from the recirculating memory CD8$^+$ T cell subsets, is the downregulation in the expression of the transcription factor KLF2 and its target gene *S1PR1*, as well as CC-chemokine receptor 7 (CCR7), which prevents their recirculation. This arrest in recirculation is accompanied by an upregulation in the expression of surface molecules that function as tissue retention receptors, such as CXC-chemokine receptor 6 (CXCR6), CXCR3, CD69, CD103 or CD49a. These phenotypic markers for CD8$^+$ T$_{RM}$ cells, along with key transcription factors regulating their function, are highlighted and further explained in Table 2 and reviewed elsewhere in greater detail[2,58,59].

Decoding soluble immune mediators

Until not long ago, the precise factors influencing tissue-specific programs of residency have remained elusive. It is now accepted that the T$_{RM}$ cell phenotype is a product of both the differentiation state and the numerous environmental cues. Moreover, although initial antigen-dependent activation can potentiate intrahepatic T$_{RM}$ cell differentiation and abundance, a range of soluble mediators, the local microbiota, cellular interactions and physical cues (independent of antigen recognition) are subsequently required to maintain residency[20,60–62].

Box 1 | *Strange Case of Dr Jekyll and Mr Hyde* by Robert Louis Stevenson, 1886

A *Strange Case of Dr Jekyll and Mr Hyde* is a defining piece of English literature — a gothic novella set in the city of London in mid-nineteenth century England, exploring the interplay between good and evil in human nature. The narrative tells the story of Dr Jekyll, a kind and well-respected scientist, who experiments with the complexities of science with a chemical concoction to separate the two sides of his personality, allowing him to transform into Mr Hyde, his sinister alter ego.

As the story unfolds, driven by a desire to explore the duality of human nature, Dr Jekyll tries to control his alter ego, and for a while, Dr Jekyll holds the power, managing to suppress his darker alter ego. Eventually, however, the story culminates in Dr Jekyll becoming addicted to the evil character and nature of Mr Hyde, and he takes one last concoction, sealing his fate as Mr Hyde forever.

This Robert Louis Stevenson novella and its effective metaphor, in which two sides of the same entity can manifest in different behaviours and actions, was the inspiration for this Review article. Here we use the phrase and themes of '*Strange Case of Dr Jekyll and Mr Hyde*' to discuss the different functional response modes of tissue-resident memory CD8$^+$ T cells in the liver, which result in either tissue-compartmentalized protective or pathogenic cellular responses.

Soluble mediators are well-characterized environmental signals required for inducing tissue residency in CD8$^+$ T cells, with IL-15 having a key role. Alongside its role in supporting the metabolism and long-term maintenance of circulating memory T cells[63–67], liver CD8$^+$ T$_{RM}$ require IL-15 for their derivation, and was first shown in IL-15-deficient mice, which lack endogenous hepatic T$_{RM}$ cells capable of mounting effective immune responses[20]. Similarly, removal of IL-15 transpresentation (via depletion of CD215; also known as IL-15Rα) or strategies to prevent CD8$^+$ T cell sensing of IL-15 substantially affected T$_{RM}$ cell maintenance in other tissues, such as the kidney[68]. Furthermore, the addition of IL-15 in combination with transforming growth factor-β (TGFβ) to human peripheral blood mononuclear cells can induce a de novo population of T$_{RM}$-like cells with high expression levels of tissue retention molecules (for example, CD69) and liver-relevant chemokine receptors (CXCR3 and CXCR6). Such CD8$^+$ T$_{RM}$-like cells exhibit similar functionality to that observed ex vivo[12,69], making these in vitro model systems useful to study factors influencing the balance between protective and pathogenic hepatic CD8$^+$ T$_{RM}$ cells.

In addition to IL-15, TGFβ has emerged as a key conductor of tissue residency, despite generally being considered a powerful suppressor of immune responses. TGFβ – produced in an inactive form complexed with the latency-associated peptide – requires integrin activation for bioactivity to epigenetically and transcriptionally alter tissue-infiltrating CD8$^+$ T cells. Specifically, TGFβ induces the expression of chemokine receptors and adhesion molecules, promoting tissue tethering, including the upregulation of CD103 (also known as integrin αE) expression, via SMAD3 binding to the *ITGAE* gene locus[70,71]. Acting as a prototypical tissue-resident T cell marker, CD103 binds to E-cadherin, which is widely expressed on biliary epithelial cells and hepatocytes[72,73]. In addition, TGFβ also enhances the expression levels of the collagen-binding integrin CD49a (also known as integrin α1) on in vitro activated CD8$^+$ T cells

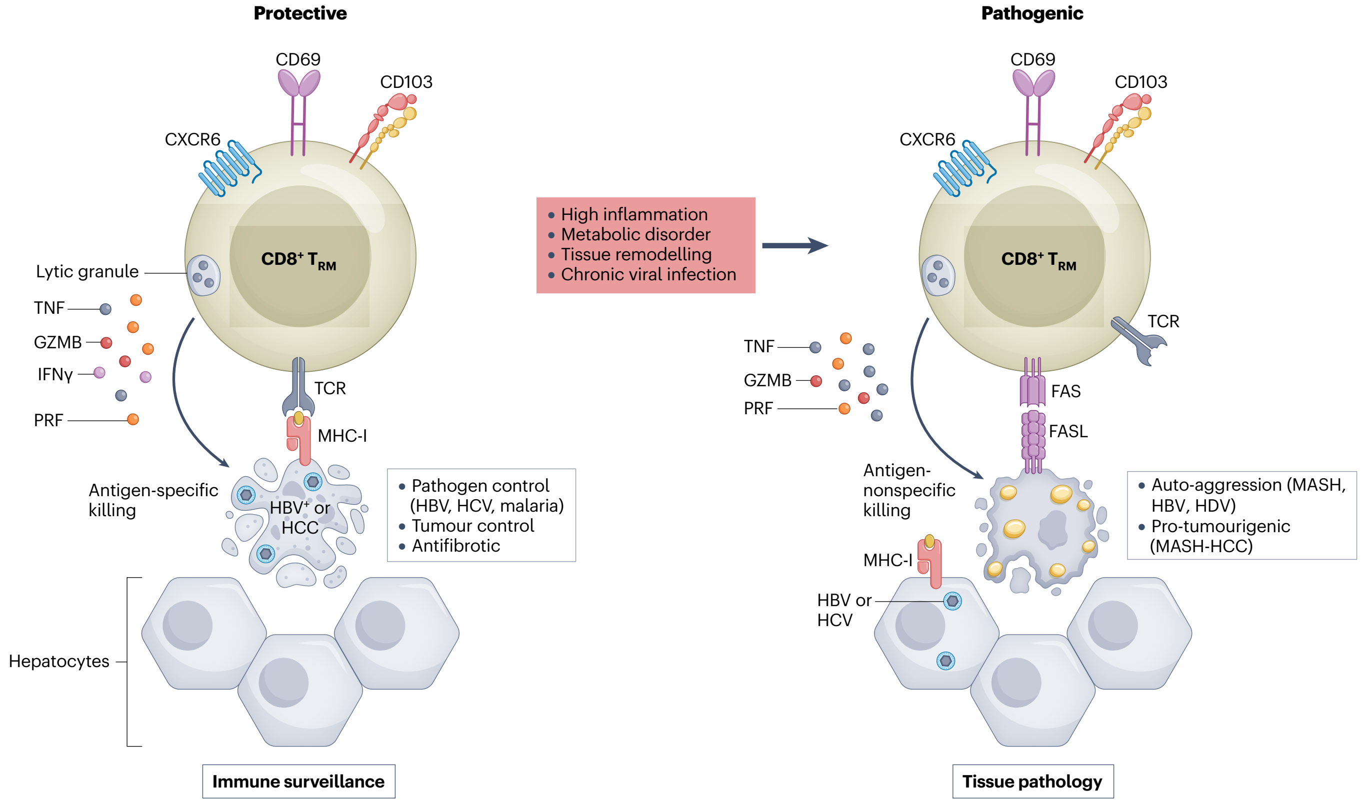

Fig. 1 | Protective 'Jekyll' and pathogenic 'Hyde' roles of hepatic CD8$^+$ T$_{RM}$ cells. Hepatic tissue-resident memory CD8$^+$ T (CD8$^+$ T$_{RM}$) cells can rapidly mount localized immune responses due to their ability to produce large quantities of cytokines and chemokines upon antigen recognition via their T cell receptor (TCR). In their protective or Jekyll response mode, they correlate with improved patient outcomes in chronic infections, malaria and hepatocellular carcinoma (HCC) by efficiently eliminating infected or malignant cells. In addition, their ability to kill activated hepatic stellate cells (myofibroblasts) contributes to fibrosis resolution. However, in their pathogenic or 'Hyde' response mode, CD8$^+$ T$_{RM}$ cells can mediate antigen-independent hepatocyte killing in chronic hepatitis B virus (HBV), chronic hepatitis D virus (HDV) and mouse models of metabolic dysfunction-associated steatohepatitis (MASH). GZMB, granzyme B; HBV, hepatitis B virus; HCV, hepatitis C virus; MHC-I, MHC class I; PRF, perforin.

and contributes to the suppression of S1P receptor 1 (S1PR1) expression via repression of KLF2 upon antigenic encounter[74–76]. Of note, although the responsiveness of CD8$^+$ T$_{RM}$ cells in many tissues to TGFβ is regulated by TGFβRII expression, which is influenced by P2RX7-dependent sensing of extracellular ATP (eATP) and nicotinamide adenine dinucleotide, forced TGFβRII expression on P2RX7-deficient CD8$^+$ T cells is insufficient to restore sensitivity to TGFβ and induce hepatic T$_{RM}$ formation in mice. This suggests that hepatic CD8$^+$ T$_{RM}$ derivation may require additional P2RX7-regulated signals beyond promoting TGFβ sensitivity[77,78]. Furthermore, in mice, expression levels of CD11a — a component of integrin lymphocyte function-associated antigen 1 (LFA1) required for CD8$^+$ T$_{RM}$ development — diminish on TGFβ-stimulated hepatic CD8$^+$ T cells[79,80]. These findings underscore the unique role of the liver microenvironment in shaping the development of hepatic CD8$^+$ T$_{RM}$.

Beyond regulating integrin expression levels, TGFβ has a crucial role in balancing CD8$^+$ T cell responsiveness by inducing key checkpoint inhibitory molecules, for example, PD1, CD39, TIM3 and TIGIT, while still preserving IFNγ-mediated protective responses upon antigen recognition on infected cells[12,79,81]. In the skin, emerging mechanistic insights in mice have shed light on how TGFβ enhances effective CD8$^+$ T cell immunity. Skin-resident CD8$^+$ T cells compete for integrin-activated bioactive TGFβ, driving the selective retention of the functionally fittest T$_{RM}$ cells when TGFβ bioavailability is limited during steady state[82]. This competition promotes an increased presence of antigen-specific 'protective' clones within the tissue while replacing newly recruited bystander T cells, thereby refining the local T$_{RM}$ cell pool for optimal immune defence.

Of note, despite the widespread expression of TGFβ across tissues[83], CD103 expression on T$_{RM}$ cells is not universal. In mice, although the majority of CD8$^+$ T$_{RM}$ cells in the gut express CD103, liver T$_{RM}$ cells often lack CD103 (refs. 17,79,80,84). Instead, they predominantly express CD49a and the adhesion molecule LFA1 for retention[80]. In humans, however, a small but important subset of hepatic CD8$^+$ T$_{RM}$ cells express CD103 in combination with CD69 and other markers of retention[12–14,26,85] (Table 2). One explanation for this difference could be the differential expression levels of E-cadherin on mouse hepatocytes across the liver[86]. In addition, mice housed under specific pathogen-free conditions have limited exposure to environmental pathogens, resulting in fewer antigen-experienced CD44$^+$ memory CD8$^+$ T cells expressing the IL-2RB chain (also known as CD122) and, therefore, are less likely to respond to IL-15 signalling in tissues, including the liver[62]. Consequently, lower numbers of IL-15-exposed CD8$^+$

T cells come into contact with TGFβ, diminishing the development of CD103^{+} T$_{\text{RM}}$ cells. In addition, environmental organ-specific factors could contribute to the phenotypic and functional disparities observed between mouse and human liver CD8^{+} T$_{\text{RM}}$ cells (Table 2). Emerging studies have begun to explore the concept that, in mice, hepatic CD8^{+} T$_{\text{RM}}$ cells are regulated independently of TGFβ[79,84,87]. Accordingly, retinoic acid, a derivative of vitamin A esterified and stored in the liver, has been proposed as a factor required to promote liver residency in CD8^{+} T cells, shaping T$_{\text{RM}}$ cell abundance, phenotype and function[87]. Importantly, retinoic acid circumvents the canonical dependence on TGFβ of CD8^{+} T$_{\text{RM}}$ cells in other tissues in mice and can fine-tune the balance between the quantity and quality of CD8^{+} T$_{\text{RM}}$, reducing production of pro-inflammatory mediators and minimizing immune-mediated tissue damage at barrier sites exposed to an abundance of external stimuli, especially microbial stimuli, which are abundant in the liver[87].

Given that both IL-15 and TGFβ signalling are involved in all stages of liver disease progression – from initial injury through inflammation and fibrosis, to cirrhosis and cancer – it is crucial to understand their effects, particularly when their concentrations are increased in the tissue. For instance, in mice and humans, the context of many chronic liver diseases, including MASH and fibrosis, in which the concentrations of TGFβ are elevated, but retinoic acid levels are diminished[88,89], the effect on hepatic CD8^{+} T$_{\text{RM}}$ cell behaviour becomes particularly important. It is plausible that as injured HSCs transdifferentiate into myofibroblasts, producing more TGFβ and upregulating integrins (for example, $\alpha_v\beta_8$ and GARP (also known as LRC32)) that cleave latent TGFβ into its bioactive form[90], CD8^{+} T$_{\text{RM}}$ cell accumulation in the liver could be substantially altered. Furthermore, heightened IL-15 signalling in MASH livers has been shown to increase the numbers of CXCR6^{+}CD8^{+} T cells with auto-aggressive functions, in mice and humans, even in the presence of increased TGFβ levels[37], demonstrating how the relative levels of local mediators in the tissue can influence the balance between protective and pathogenic hepatic CD8^{+} T$_{\text{RM}}$ cells.

Dissecting the cellular network

Beyond soluble differentiation factors, it is evident that the functional response mode of CD8^{+} T$_{\text{RM}}$ within the liver and other tissues is shaped by contact-dependent interactions. The complexity of this network is best exemplified by the coordinated involvement of both immune (myeloid) and non-immune (stromal and parenchymal) cells in IL-15 signalling, which is essential for the development, maintenance and function of hepatic CD8^{+} T$_{\text{RM}}$ cells[20,69,91]. Unlike classical cytokine signalling mechanisms, in which soluble mediators such as TGFβ or IL-10 bind to receptors on target cells[92], IL-15-driven CD8^{+} T$_{\text{RM}}$ cell differentiation relies on a contact-dependent process. Specifically, soluble IL-15 must be presented in *trans* by cells expressing IL-15RA on their surface[93]. The development and function of hepatic CD8^{+} T$_{\text{RM}}$ cells depend not only on the quality of signalling cues but also on their spatial positioning within the unique liver environment. As CD8^{+} T cells enter the liver via the portal tract, they engage in dynamic interactions with

Table 1 | Key studies highlighting the functional role of hepatic CD8^{+} T$_{\text{RM}}$ cells

Disease	Role	Species	Phenotype	Function	Refs.
Protective CD8^{+} T$_{\text{RM}}$ cells ('Jekyll')					
HBV-HCC	Tumour control	Human	CD69^{+}CD103^{+}	Enrichment of CD8^{+} T$_{\text{RM}}$ cells in HBV-related HCC and association with improved patient prognosis	22–24
HBV infection	Viral control	Human	CD69^{+}CD103^{+}	Correlation of CD8^{+} T$_{\text{RM}}$ cells (capable of potently producing antiviral mediators) with viral control	12
Malaria	Protective immunity	Mouse	CD69^{+}LFA1^{+}CXCR3^{+}CXCR6^{+}	Induction of vaccine-mediated protective immunity against sporozoite challenge via cytokine-mediated killing of *Plasmodium*-infected cells	17,169,170
Malaria	Protective immunity	Human	CD45RA^{+}CD69^{+}CD11a$^{\text{high}}$ (T$_{\text{RM}}$-like cells)	Correlation of peripheral T$_{\text{RM}}$-like cells post-vaccination with sterile protection from liver-stage malaria by infectious mosquito bite challenge	171
MASH	Antifibrotic	Mouse	CD69^{+}CD103^{-}	FASL–FAS-mediated elimination of activated myofibroblasts promoting fibrosis resolution	25
Pathogenic CD8^{+} T$_{\text{RM}}$ cell ('Hyde')					
MASH	Liver pathology	Mouse	CXCR6^{+}CD103^{-}	IL-15-driven auto-aggression of hepatocytes through TNF and FASL–FAS	37
MASH-HCC	Pro-tumorigenic	Mouse	CXCR6^{+}PD1^{-}CD103^{-}	CD8^{+} T cell-dependent induction of HCC in MASH after PD1 blockade driven by TNF	43
HBV	Liver pathology	Human	CD69^{+}CXCR6^{+}	IL-12 and IL-2-induced CD8^{+} T cell killing of hepatocytes through FASL–FAS	31
HAV	Liver pathology	Human	CD69^{+}CD103^{-}	IL-15-driven, antigen-independent target cell killing of non-infected hepatocytes through NKG2D	27
HDV	Liver pathology	Human	CD69^{+}CXCR6^{+}	Bystander activation via cytokine-induced NKG2D-dependent cytotoxicity	28
AIH	Liver pathology	Human	CD69^{+}CD103^{+}	IL-15 and TGFβ-driven accumulation of hepatic CD8^{+} T$_{\text{RM}}$ cells correlate with AIH disease severity	39

AIH, autoimmune hepatitis; CXCR, CXC-chemokine receptor; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; LFA1, lymphocyte function-associated antigen 1; MASH, metabolic dysfunction-associated steatohepatitis; TGFβ, transforming growth factor-β; T$_{\text{RM,}}$ tissue-resident memory T.

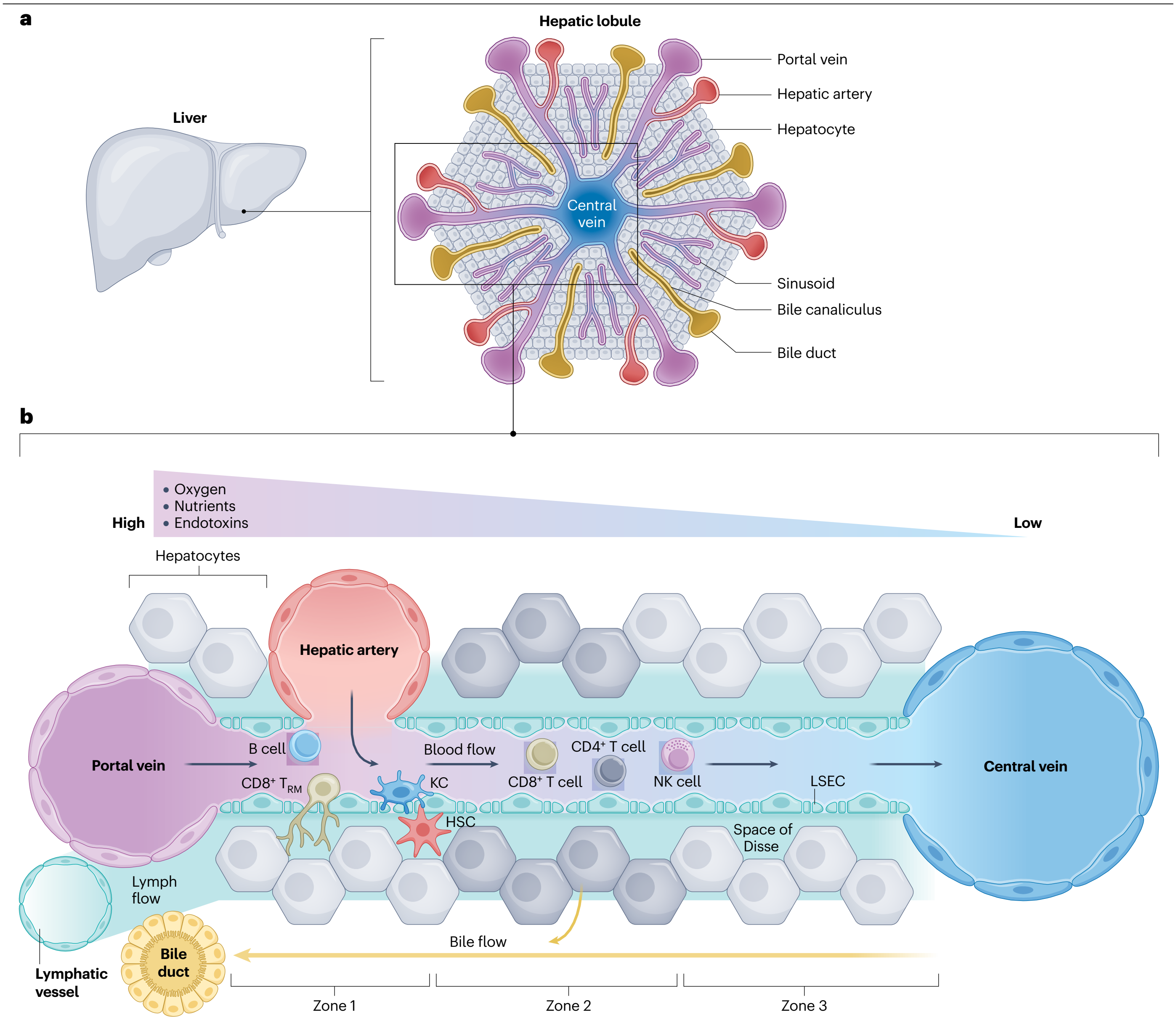

Fig. 2 | Schematic representation of the micro-architecture of a liver lobule. **a**, The liver receives a dual blood supply from the hepatic artery and the portal vein. The hepatic artery delivers oxygenated blood, whereas the portal vein brings nutrient-rich, deoxygenated blood from the gastrointestinal tract. **b**, Liver lobules are organized around portal tracts, which contain branches of the hepatic artery, portal vein, bile ducts, lymphatic vessels and associated stromal elements. Blood from the hepatic artery and portal vein flows through the liver sinusoids towards the central vein, exiting the liver via the hepatic veins. Bile secreted by hepatocytes is collected into bile ducts within the portal tracts and transported to the gallbladder. Liver sinusoidal endothelial cells (LSECs), characterized by fenestrations, line the sinusoids and facilitate immune surveillance by tissue-resident CD8$^+$ T (CD8$^+$ T$_{RM}$) cells within the vascular space. Hepatic stellate cells (HSCs) reside in the space of Disse, which also connects to the lymphatic network. Additional immune cell populations, including Kupffer cells (KCs), B cells and natural killer (NK) cells, are distributed throughout the liver to maintain local immune homeostasis.

myeloid cells, hepatocytes, LSECs and HSCs, each of which exerts distinct immunomodulatory effects that could regulate surface molecule expression[94,95]. For example, in mice, hepatocytes presenting viral antigens drive the upregulation of PD1 expression on CD8$^+$ T cells[15], whereas the interaction with CXC-chemokine ligand 16 (CXCL16)-producing LSECs promotes the retention of CXCR6$^+$CD8$^+$ T cells in the liver[96]. Moreover, exposure to HSC-derived soluble mediators such as IL-15 and TGFβ reinforces CD8$^+$ T$_{RM}$ cell identity in humans by inducing CD103 expression[69]. Importantly, during liver diseases with progressive injury, these cellular interactions become dysregulated as newly infiltrating pro-inflammatory MHC class II$^+$ (MHC-II$^+$) antigen-presenting cells alter the hepatic cellular network and potentially engage with memory

$CD8^+$ T cell subsets within periportal areas, thereby preferentially promoting their differentiation into pathogenic $CD8^+$ T_{RM} cells[97–100]. Exemplifying the plasticity of MHC-II^+ antigen-presenting cells in the liver, Kupffer cells exposed to IL-2 acquire the capacity to convert tolerized $CD8^+$ T cells into functional antiviral T cells during chronic viral liver infection in mice[101]. These findings highlight the critical

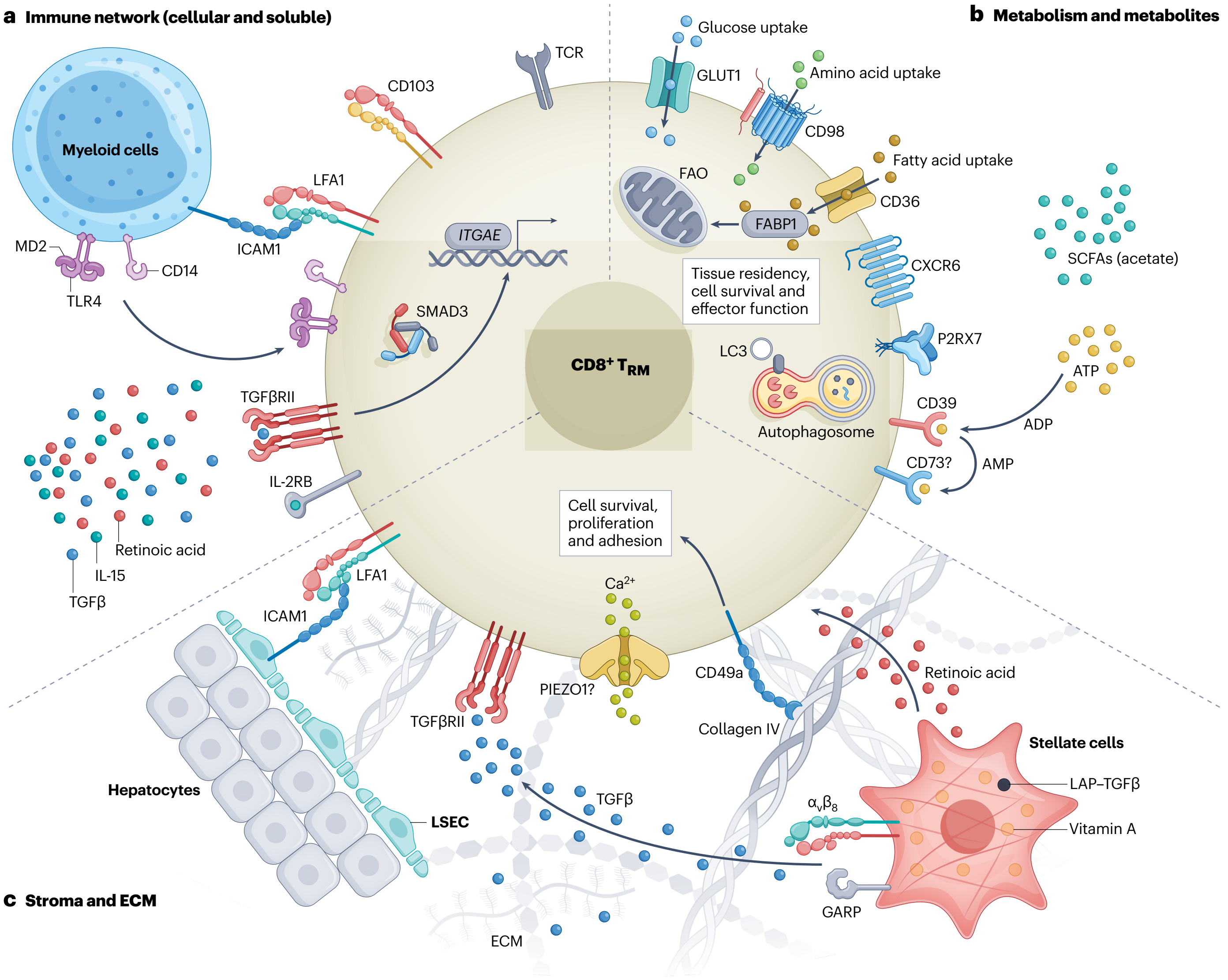

Fig. 3 | Environmental cues modulating $CD8^+$ T_{RM} cell phenotype and function. $CD8^+$ tissue-resident memory T (T_{RM}) cells interpret, integrate (indicated by arrows) and respond to a wide range of environmental signals. **a**, Immune network influences (cellular and soluble factors) on $CD8^+$ T_{RM} cells: soluble mediators such as IL-15, transforming growth factor-β (TGFβ) and retinoic acid are crucial for the induction and maintenance of tissue-resident phenotypes. TGFβ promotes chemokine receptor and adhesion molecule expression (for example, CD103) via SMAD3 binding to the *ITGAE* locus. T cells can acquire components of neighbouring myeloid cell plasma membranes (CD14, Toll-like receptor 4 (TLR4) and myeloid differentiation protein 2 (MD2)) upon contact-dependent interaction, endowing them with unique characteristics, such as increased turnover and responsiveness to bacterial lipopolysaccharide. **b**, Metabolic cues regulating T_{RM} phenotype and function: liver $CD8^+$ T_{RM} cells express high levels of glucose transporters (such as glucose transporter 1 (GLUT1)), amino acid transporters (such as CD98) and fatty acid transporters, along with tissue-specific fatty acid-binding proteins (such as fatty acid-binding protein 1 (FABP1)), ensuring uptake of key nutrients to fuel T cell-intrinsic metabolic pathways. Metabolic stimuli, such as extracellular ATP or acetate, can trigger auto-aggressive responses, leading to nonspecific hepatocyte killing. **c**, Stromal and extracellular matrix (ECM) interactions shaping $CD8^+$ T_{RM} cell identity: liver $CD8^+$ T_{RM} cell function and retention are influenced by interactions with liver sinusoidal endothelial cells (LSECs) and hepatic stellate cell (HSC)-derived soluble mediators, which induce the expression of CXC-chemokine receptor 6 (CXCR6) and CD103, respectively. HSCs not only produce TGFβ but also express the integrins (GARP and $\alpha_v\beta_8$) necessary for its bioactivation. TGFβ enhances the expression of the collagen-binding integrin CD49a, which contributes to T_{RM} cell survival and function in a tissue-specific manner. In addition, increasing evidence suggests that mechanosensing, mediated by receptors such as PIEZO1, and its ability to modulate lymphocyte function-associated antigen 1 (LFA1) expression levels, might have a role in T cell retention and function[114]. ADP, adenosine diphosphate; AMP, adenosine monophosphate; FAO, fatty acid oxidation; ICAM1, intercellular adhesion molecule 1; LAP, latency-associated peptide; SCFA, short-chain fatty acid; TCR, T cell receptor.

Table 2 | T_{RM} cell marker expression in the mouse and human liver

Location	Marker	Mouse		Human		Role in retention
		Liver-infiltrating T cells	Liver T_{RM}	Liver-infiltrating T cells	Liver T_{RM}	
Surface receptors	CD69	X	✓	X	✓	Sequestration of S1PR1 that mediates egress of T cells
	CD103	X	X	X	X or ✓	Binds to epithelial cell-expressed E-cadherin
	CD49a	X	✓	X	✓	Binds to collagen; associated with homing to non-lymphoid tissues
	CX3CR1	✓	X	✓	X	Receptor for the chemokine fractalkine (CX3CL1): discriminates memory CD8$^+$ T cells with cytotoxic effector functions
	CXCR6	X	✓	X	✓	Receptor for the chemokine CXCL16; controls tissue distribution and survival of T_{RM} cells
	CXCR3	X	✓	X	✓	Receptor for the chemokines CXCL9, CXCL10 and CXCL11; preferentially expressed on activated CD8$^+$ T cells and necessary for tissue homing
	S1PR1	✓	X	✓	X	Receptor for the lipid S1P; controls T cell egress, migration and localization
	CCR7	✓	X	✓	X	Promotes recirculation of naive T cells through secondary lymphoid organs
Transcriptional regulators	Hobit	X	✓	✓	X	Controls the differentiation and maintenance of T_{RM} cells
	Blimp1	X	✓	X	✓	Promotes T_{RM} cell formation, suppresses tissue exit pathways in T_{RM} cell precursors and contributes to T_{RM} cell maintenance
	KLF2	✓	X	✓	X	Negative regulator of S1PR1; regulates T cell trafficking, quiescence and differentiation
	T-bet	✓	X	✓	X	Essential for IL-15 receptor expression and T cell survival

CCR7, CC-chemokine receptor 7; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; CX3CL1, CX3C-chemokine ligand 1; CX3CR1, CX3C-chemokine receptor 1; T_{RM}, tissue-resident memory T; S1P, sphingosine-1-phosphate; S1PR1, S1P receptor 1.

interplay between immune cells and neighbouring cells in shaping the differentiation and function of hepatic CD8$^+$ T_{RM} cells.

Beyond their role in CD8$^+$ T_{RM} cell differentiation, stromal cells also regulate hepatic CD8$^+$ T_{RM} function by suppressing excessive pro-inflammatory activity through PD1 engagement. This interaction helps to maintain immune homeostasis within the liver[102,103]. However, despite marked expression levels of PD1, liver-resident CD8$^+$ T cells remain highly functional, retaining cytotoxic capacity and the ability to rapidly produce cytokines such as IFNγ and TNF[12,37,85]. These observations suggest that, in the liver, PD1 expression levels by CD8$^+$ T_{RM} cells are not necessarily indicative of classical T cell exhaustion. Among stromal cells, HSCs have emerged as an important immunological hub due to their potent ability to provide key regulatory molecules through membrane exchange. For example, in mice, HSCs can transfer MHC class I (MHC-I) molecules to LSECs, enhancing cross-presentation and contributing to antiviral CD8$^+$ T cell immunity[104]. In addition, human HSCs have been shown to facilitate the donation of myeloid cell membrane components such as CD14, Toll-like receptor 2 (TLR2) and TLR4 to CD8$^+$ T cells[105] (Fig. 3). Human CD14 co-expressing CD8$^+$ T_{RM} cells seem to accumulate in zone 2, suggesting that, in the mid-lobular region of the liver, cell interactions between CD8$^+$ T_{RM} cells and CD14^{high} myeloid cells are favoured[105]. Fascinatingly, myeloid-reprogrammed CD8$^+$ T cells, distinguished by co-expression of CD14 and CD8, exhibit unique characteristics with heightened turnover, immunomodulatory effector function through the constitutive production of immunoprotective cytokines (IL-2 and IL-10) and exert rapid and potent effector function upon antigenic stimulation[105]. In the presence of Gram-negative bacteria or bacteria-derived products, these highly adapted CD8$^+$ T_{RM} cells transition to chemotactic and hepatoprotective roles by producing soluble mediators such as IL-8, IL-6 and IL-33 (ref. 105). The concept that CD8$^+$ T cells can acquire superior functions through the transfer of myeloid-derived immunoregulatory constituents is particularly compelling in light of a synthetic gain-of-function screen in primary human CD8$^+$ T cells[106]. This study demonstrated that overexpression of membrane receptors typically expressed on myeloid cells, such as the lymphotoxin B receptor, induced profound epigenomic remodelling leading to potent effector function and resistance to chronic stimulation[106]. Myeloid reprogrammed, hyperfunctional CD8$^+$ T_{RM} cells could represent an effective hepatoprotective firewall against infiltrating bacteria (for example, *Escherichia coli* or *Salmonella*[107]). However, it remains to be elucidated whether such cells represent an appropriate therapeutic target in chronic liver disease.

Integrating mechanical and physical stimuli

A distinguishing feature of hepatic CD8$^+$ T_{RM} cells compared with T_{RM} cells from other non-lymphoid organs is their ability to lodge and migrate through the sinusoids, rather than the parenchyma. Owing to their strategic location, circulating hepatic CD8$^+$ T_{RM} cell precursors have little need to actively exit the bloodstream to acquire a resident profile. Despite remaining resident for up to a decade, liver CD8$^+$ T_{RM} cells are not stationary. Patrolling CD8$^+$ T_{RM} cells move through the sinusoids with a median speed of approximately 10 μm per minute[80] — a rate equivalent to CD8$^+$ T_{RM} in other organs[108]. Upon antigen recognition, hepatic CD8$^+$ T cells can arrest independently of blood flow and direction[109,110], extending dendrite-like pseudopodia to probe the underlying parenchyma through the fenestrated endothelium. Critically, these sinusoidal fenestrations are progressively lost during LSEC capillarization in fibrosis[111,112]. Such morphological changes directly impair the ability of hepatic CD8$^+$ T_{RM} cells to access and sample the parenchyma, thereby limiting antigen-specific activation[110]. In addition, the motility and parenchymal sampling rate of a CD8$^+$ T$_{RM}$ cell is substantially reduced by fibrillar ECM accumulation (such as collagen I, collagen III, elastin and fibronectin). Although it has not yet been shown for CD8$^+$ T$_{RM}$ cells patrolling the liver, the motility of mouse uterine perimetrium T$_{RM}$ cells reduces to approximately 6 µm per minute in collagen-dense regions[108]. Hence, LSEC capillarization and ECM accumulation in chronic liver disease might substantially hinder the ability of hepatic CD8$^+$ T$_{RM}$ cells to efficiently survey and respond to pathogens or malignancies within the liver and increase the likelihood of CD8$^+$ T$_{RM}$ cells responding to activating signals that could result in tissue damage.

During their patrol of tissues, CD8$^+$ T cells interact directly with the surrounding ECM and, therefore, encounter mechanical forces, including stiffness and viscoelasticity (stress exerted from deformation)[56,57]. These forces are integrated into cellular mechanosensing and mechanotransduction pathways, shaping both the phenotype and the function of CD8$^+$ T$_{RM}$ cells. In a single-cell RNA sequencing analysis of tumour, adjacent normal tissue and blood from individuals with HCC, the stiffness and viscoelasticity of the liver microenvironment were shown to considerably alter T cells at the transcriptional level[56]. Specifically, modifications to ECM viscoelasticity through collagen crosslinking, more than stiffness, result in increased T cell activation and rapid responsiveness to antigen, features similar to those of a highly functional CD8$^+$ T$_{RM}$ cell[56]. By contrast, other studies using in vitro activated CD8$^+$ T cells have demonstrated that increasing environmental stiffness drives an exhausted and dysfunctional profile, marked by decreased cytokine production (for example, IFNγ and TNF) and enhanced expression of co-inhibitory receptors (for example, PD1 and TIM3)[57]. Previous preclinical and clinical work — although not specifically in the liver — has also shown that T cell integrin density is sensitive to molecular-scale mechanical forces[113]. For example, genetic ablation in vitro of the mechanosensor PIEZO1 on human CD4$^+$ and CD8$^+$ T cells disrupts expression of LFA1 (ref. 114), highlighting a key role for mechanosensing in T cell retention and function. This capacity to interpret mechanical cues from the local environment probably contributes to the retention and function of CD8$^+$ T$_{RM}$ cells within liver sinusoids through mechanosensors such as PIEZO1 or PIEZO2, or other yet unidentified mechanosensors (Fig. 3). However, exactly how hepatic CD8$^+$ T$_{RM}$ cells respond to dynamic changes in their mechanical environment remains an open question.

Beyond the mechanosensitive effects arising from interactions with the endothelium and ECM, both resident and infiltrating CD8$^+$ T cells in the liver could be shaped by the composition of the matrisome — the ensemble of ECM components and associated proteins that interact with or are structurally integrated into the ECM. Given their role in transmitting extracellular signals into the cell ('outside-in' signalling[95]), CD49a and CD103 are key mediators of cell–cell and cell–ECM interactions[115]. These interactions are crucial not only for determining the precise in situ localization of CD8$^+$ T$_{RM}$ cells but also for shaping their function. For example, in the mouse lung, the collagen I-binding and collagen IV-binding integrin CD49a enhances CD8$^+$ T$_{RM}$ cell survival by reducing apoptosis and promoting local motility[115,116]. By contrast, in the skin, CD49a expression defines a functionally distinct, cytotoxic subset of CD8$^+$ T$_{RM}$ cells characterized by constitutively higher levels of perforin and granzyme B, which contribute to immunopathology[74,75]. Furthermore, the matrisome acts as a reservoir for CD8$^+$ T$_{RM}$ cell survival factors, sequestering cytokines and growth factors (for example TGFβ, hepatocyte growth factor (HGF), CXCL12 and vascular endothelial growth factor (VEGF)) involved in T cell migration, proliferation and differentiation[117], and can impose tight regulation over the activation and activity of mediators such as TGFβ.

Despite its well-documented roles in other tissues, the functional importance of CD49a in the liver remains largely unexplored. Although studies have demonstrated CD49a protein expression on hepatic CD8$^+$ T$_{RM}$ cells in both mice and humans[39,60,85], its specific contributions to CD8$^+$ T$_{RM}$ cell retention, function and precise localization within the liver microenvironment have yet to be fully elucidated. As hepatic fibrosis is characterized by excessive ECM deposition and dysregulated ECM degradation[118], it is essential to investigate how alterations in the matrisome shape the balance between protective and pathogenic hepatic CD8$^+$ T$_{RM}$ cells.

Metabolic adaptations, nutrients and metabolites as both stimuli and fuel

The liver is a highly metabolic organ with a remarkable capacity to take up and process nutrients, including glucose, amino acids and fatty acids. In the past few years, the importance of cellular metabolism to dictate CD8$^+$ T cell differentiation and function has come to the forefront, including how metabolic programs within a cell are modulated by exogenous nutrient gradients and the need for metabolic adaptations within tissues to promote longevity and function. Particularly in nutrient-competitive tissues such as the liver, nutrients and metabolites fuelling CD8$^+$ T cell metabolism are now often defined as crucial regulators capable of interacting with the classical three-signal model of T cell activation: (1) T cell receptor (TCR) binding to antigen, (2) the requirement for co-stimulation, and (3) the addition of cytokine signals. Thus, nutrients and metabolites are postulated as 'signal 4' in licensing T cell immunity[55,119].

To interpret and incorporate signal 4, CD8$^+$ T$_{RM}$ cells in the liver express a range of nutrient transporters permitting the uptake of vital nutrients, including glucose transporter 1 (GLUT1; also known as SLC2A1) facilitating glucose transport[120], CD71 the transferrin receptor essential for iron uptake, CD36 a protein involved in the import of long-chain fatty acids (LCFAs)[105] and FABP1 (also known as liver-type fatty acid-binding protein) also involved in the binding, transport and metabolism of LCFAs[121] (Fig. 3). Expression of FABP isoforms by CD8$^+$ T$_{RM}$ cells are organ-specific, adapting to the local niche, and so represent one pathway of environmental cues specific to each tissue[121]. Furthermore, by way of a compensatory mechanism to local L-arginine restriction in the liver driven by arginase-I-producing cells, hepatic CD8$^+$ T$_{RM}$ cells increase the expression levels of CD98, involved in the uptake of neutral amino acids[122,123] and kynurenine[124], required to underpin the response to antigen[122]. Expression of such amino acid transporters on hepatic CD8$^+$ T$_{RM}$ cells requires local antigenic stimulation or exposure to pro-inflammatory cytokines. Cytokines involved in sustaining high expression levels of CD98, including the CD8$^+$ T$_{RM}$ cell differentiation factor IL-15, and IL-2, which is produced at high levels in an autocrine manner by liver CD8$^+$ T$_{RM}$ cells[122,125]. A combination of in vitro and in vivo experimental models has demonstrated that autophagic flux and the ability of a T cell to recycle rate-limiting nutrients and/or mitochondrial remodelling are controlled by amino acid sensing, and therefore the associated levels of key transporters[126]. Uptake through hepatic CD8$^+$ T$_{RM}$ cell amino acid transporters can fuel mitochondrial remodelling in line with hepatic CD8$^+$ T$_{RM}$ cells harbouring less dysfunctional depolarized mitochondria than liver-infiltrating non-resident T cells[69]. Moreover, liver CD8$^+$ T$_{RM}$ cells exhibit increased expression levels of LC3 (ref. 69), a protein indispensable for the cellular recycling process of autophagy[127]. It remains to be determined for CD8$^+$ T$_{RM}$ cells in conditions of nutrient restriction, such as the human liver, whether this represents an accumulation of autophagosomes and autophagic cargo as a result of repressed flux due to enhanced nutrient transporter expression[126], or whether this suggests that CD8$^+$ T$_{RM}$ cells require enhanced recycling and active flux to survive hostile environments[69].

Anatomically, receiving 75–80% of its blood via the portal vein (Fig. 2), the liver is continuously exposed to deoxygenated blood enriched with waste products and microbial-derived antigens from the gut. Consequently, in addition to its nutrient-competitive environment, the liver has evolved multiple immunosuppressive mechanisms to prevent excessive immune reactions. As one example, proliferation and effector function of hepatic CD8$^+$ T$_{RM}$ cells are dampened by the catabolism of essential amino acids through the activity of indoleamine 2,3-dioxygenase and arginase-I in the liver[123,128]. Of note, under homeostatic conditions, the surveillance capacity of hepatic CD8$^+$ T$_{RM}$ cells is still intact. However, in CHB, hepatic CD8$^+$ T$_{RM}$ become dysfunctional through additional immunosuppressive mechanisms, which are, in part, driven by interactions with inhibitory immune cells, such as myeloid-derived suppressor cells or endothelial cells. It was shown with a combination of in vitro experiments and mouse models, for example, that myeloid-derived suppressor cells directly suppressed CD8$^+$ T cell effector functions through transfer of the dicarbonyl methylglyoxal in a cell–cell contact-dependent manner[129] and through depletion of L-arginine by high arginase-I expression[123].

A study published in 2024 demonstrated that prolonged interaction with endothelial cells impairs TCR functionality in liver-resident HBV-specific CXCR6$^+$CD8$^+$ T cells during CHB, and this dysfunction is mediated through an adenylyl cyclase-dependent mechanism[95]. A potential inducer of cyclic AMP signalling upstream of adenylyl cyclase activity is prostaglandin E2 — a polyunsaturated fatty acid derived from arachidonic acid — that has been shown to be elevated in the liver tissue of patients with CHB[130]. By contrast, the short-chain fatty acid acetate has been shown to potently enhance the effector function of hepatic CXCR6$^+$CD8$^+$ T cells, leading to auto-aggression in MASH[37]. Importantly, given the reliance of CD8$^+$ T$_{RM}$ cells on exogenous fatty acid uptake to fuel fatty acid oxidation (FAO) as their primary energy source[131], and the observation that oxidized low-density lipoproteins or LCFAs can impair immune cell function[132,133], it remains to be determined how different free fatty acids influence the function of hepatic CD8$^+$ T$_{RM}$ cells during liver inflammation, such as in metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as nonalcoholic fatty liver disease) or HCC. Understanding the extent to which different fatty acids shape the function of hepatic CD8$^+$ T$_{RM}$ cells will be critical in defining their role as protective or pathogenic CD8$^+$ T cells in the liver. Moreover, it will be essential to decipher whether nutrient-driven immunomodulation affects hepatic CD8$^+$ T$_{RM}$ cells in an antigen-specific manner during viral infections and tumours. Such specificity has already been reported for the effect of bile acids on tumour-specific CD8$^+$ T cells in mouse models of HCC, in which both primary and secondary bile acids selectively suppressed CD8$^+$ T cell effector functions[37,134]. However, whether specific bile acids could instead enhance the effector function of bystander hepatic CD8$^+$ T$_{RM}$ cells, which have been shown to be highly cytotoxic in PSC[135,136], remains to be determined.

A similar antigen-specific dependency of hepatic CD8$^+$ T$_{RM}$ cells was observed in the context of P2RX7-mediated sensing of eATP[37]. This study revealed that inhibiting P2RX7 activity in mice selectively prevented CD8$^+$ T cell auto-aggression while preserving antigen-specific immunity, supporting the Jekyll and Hyde paradigm in which the same CD8$^+$ T cell can adopt either protective or pathogenic roles depending on the local microenvironment. In line with the context-dependent role of eATP, several preclinical studies have demonstrated that the extracellular local concentration levels of ATP differentially affect hepatic CD8$^+$ T$_{RM}$ cells depending on the inflammatory milieu within the liver. Under non-inflammatory conditions, homeostatic ATP levels support CD8$^+$ T$_{RM}$ cell survival by promoting oxidative phosphorylation[77]. Conversely, eATP, which is typically degraded by CD39 and CD73 into adenosine, an immunosuppressive metabolite, provides immunoregulatory functions on liver immunity at steady state[137]. However, high ATP concentration levels in an inflammatory environment can activate CXCR6$^+$CD8$^+$ T cells, leading to auto-aggressive responses or even cell death in hepatic CD8$^+$ T$_{RM}$ cells[138]. These findings underscore the context-dependent role of eATP and its degradation products, demonstrating how metabolite concentrations can shape the functional state of hepatic CD8$^+$ T$_{RM}$ cells, influencing their survival, activation or suppression based on the degree of tissue damage within the liver microenvironment.

The unique architecture of the liver and the venous, low oxygenated blood supply previously mentioned also mean that CD8$^+$ T$_{RM}$ cells are exposed to differential oxygen gradients depending on location, especially during the progression of fibrotic liver disease, in which it is both a driver of fibrosis and a consequence of it[139]. T cell function is affected by hypoxia-inducible factors (HIFs)[140], and interestingly, HIF signalling increases responsiveness to TCR stimulation[141]. In an in vitro setting, hypoxia can synergistically help to induce a CD8$^+$ T$_{RM}$ cell phenotype in conjunction with TGFβ[142]. In the case of the liver, expression of HIF2A has also been shown to license a subset of CD69$^+$CD103$^-$ T$_{RM}$ cells to bystander cytotoxicity, promoting local tissue damage, driving liver pathology[85].

Together, metabolic cues in the liver have a pivotal role in shaping the function of hepatic CD8$^+$ T$_{RM}$ cells, and given the profound metabolic alterations that occur in liver diseases such as MASLD, PSC and primary biliary cholangitis (PBC), it is likely that additional metabolic regulators will be identified. It is highly likely that the metabolic landscape along the periportal–central axis not only influences CD8$^+$ T$_{RM}$ cell accumulation and survival but also has a decisive role in dictating whether hepatic CD8$^+$ T$_{RM}$ cells adopt protective or pathogenic roles within the liver microenvironment.

Looking beyond environmental factors

Despite the well-recognized influence of environmental factors — such as immune signalling networks, stromal interactions, ECM composition and metabolic cues — on hepatic CD8$^+$ T$_{RM}$ cells, the extent to which sex-dependent factors shape their protective or pathogenic roles remains largely unexplored. Given the well-documented biological sex (as in, sex assigned at birth) differences in liver diseases[143], it is likely that sex influences hepatic CD8$^+$ T$_{RM}$ cell function either directly, through hormonal signalling, or indirectly, via effects on the liver microenvironment. One of the most striking examples of biological sex differences in liver immunology is observed in autoimmune liver diseases. Conditions such as autoimmune hepatitis and PBC exhibit a strong female predominance, among the highest of all autoimmune diseases, suggesting a heightened susceptibility of the female liver to immune dysregulation[144]. Similarly, sex differences are evident in CHB, in which men are more prone to persistent HBV infection and associated complications, including HCC[145]. This disparity is largely attributed to the stronger antiviral immune responses observed in women who are more likely to eradicate virus-infected hepatocytes and to reduce the likelihood of persistent infection[146]. Biological sex differences in immune function are, at least in part, mediated by differential expression of TLRs on innate immune cells, variations in cytokine secretion and the reported opposing effects of biological sex hormones on T cell function[147]. Oestrogen enhances CD8$^+$ T cell responses through oestrogen receptor-β signalling[148], whereas androgens have been shown to promote CD8^+ T cell exhaustion and reduce IFNγ production, potentially impairing antiviral immunity[149]. However, the precise mechanisms through which these hormonal differences affect hepatic CD8^+ T_{RM} cells remain to be elucidated. Further research is needed to determine whether key cytokines that regulate hepatic CD8^+ T_{RM} cell function, such as IL-15 and TGFβ, are differentially influenced by biological sex hormones, as has been shown for IL-12 production by dendritic cells[150]. In addition, given that the remodelling of the ECM is differentially regulated in men and women[151], it is likely that sex-specific matrix composition could affect CD8^+ T cell retention and function in the liver under homeostatic and inflammatory conditions. Beyond immune and hormonal factors, biological sex differences in gut microbiota composition in mice (for example, *Clostridium* and *Bacteroidetes*)[152] might also contribute to hepatic CD8^+ T_{RM} cell regulation by modulating the availability of microbiota-derived metabolites that shape liver immunity. Understanding these complex interactions will be essential to understanding the influence of biological sex on the protective role of hepatic CD8^+ T_{RM} cells and, consequently, to developing sex-specific therapeutic strategies targeting hepatic CD8^+ T_{RM} cell function in liver diseases.

Another fundamental yet often overlooked layer of regulation is the influence of the circadian rhythm, which operates at both the cellular and the tissue levels. The liver exhibits robust circadian oscillations governed by systemic cues such as feeding–fasting cycles and neuroendocrine signalling, as well as intrinsic cellular clocks[153]. Circadian rhythm has long been described to have profound effects on immune cell dynamics, including cell trafficking, functional output and metabolic reprogramming[154], and altering cytokine networks. For example, TGFβ not only governs CD8^+ T_{RM} cell differentiation and homeostasis but also acts as a critical modulator of circadian rhythm, contributing to the synchronization of cellular clocks and maintaining rhythmic homeostasis. In addition, CD8^+ T cells harbour their own intrinsic circadian clock, in which clock gene oscillations regulate T cell activation and proliferation[155]. Mitochondrial metabolism and fitness, a key determinant of CD8^+ T_{RM} cell persistence, is also subject to circadian control, with oscillations in oxidative phosphorylation and FAO shaping T cell longevity. Circadian control of mitochondrial function is orchestrated through diurnal fluctuations in rate-limiting mitochondrial enzymes and nutrient utilization pathways, regulated by PERIOD proteins, a group of proteins crucial for circadian rhythm regulation[156]. Given that hepatic CD8^+ T_{RM} cells rely heavily on FAO for long-term survival, it is plausible that temporal regulation of lipid metabolism within the liver imposes a rhythmic constraint on CD8^+ T_{RM} cell bioenergetics, in which metabolic reprogramming dictates their function. Finally, chronic disruption of circadian rhythms, as observed in shift work, metabolic syndrome and chronic liver disease, has been linked to increased hepatic inflammation, fibrosis and impaired antiviral immunity[157,158]. However, the extent to which such dysregulation affects hepatic CD8^+ T_{RM} cells remains another open question. Given their role in immune surveillance and tissue integrity, it is conceivable that desynchronization of hepatic CD8^+ T_{RM} cell responses contributes to liver disease pathogenesis, potentially shifting their equilibrium towards an inflammatory or dysfunctional phenotype.

Although considerable progress has been made in delineating the role of metabolic and stromal interactions in CD8^+ T_{RM} cell homeostasis, future studies should consider the temporal dimension as an additional regulatory axis governing T_{RM} cell adaptation to the liver microenvironment. Dissecting how the circadian rhythm interacts with immune-metabolic networks might provide new insights into hepatic T_{RM} cell plasticity, with potential implications for optimizing immunotherapies and therapeutic interventions targeting liver-resident T cell populations.

Conclusions

The ability of polyfunctional CD8^+ T_{RM} cells to persist and maintain durable antigen-specific responses long term in tissues[26,159,160] has led to substantial interest in their exploitation for therapeutic manipulation, including adoptive cell therapy for solid-organ cancers such as HCC. One approach to enhance the accumulation and function in tumours of one such adoptive cell therapy – chimeric antigen receptor (CAR) T cell therapy – is to harness the ability of the soluble mediators discussed above to transcriptionally alter CD8^+ T cells, promoting CD8^+ T_{RM} cell development and long-term survival (Fig. 4). For example, provision of TGFβ during the manufacturing of CAR T cells targeting

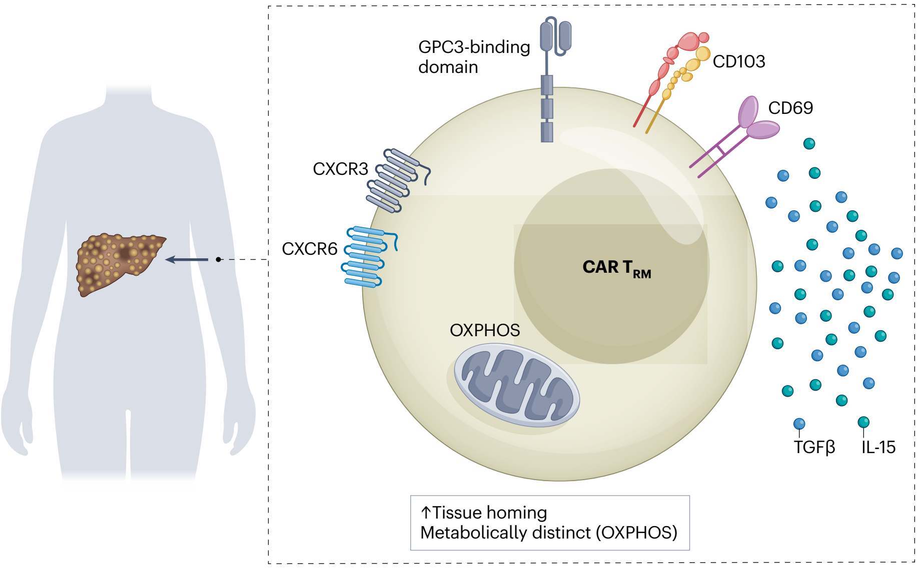

Fig. 4 | T_{RM} cell induction strategies for CAR T cell therapy. Currently, interest has emerged in leveraging tissue-resident memory T (T_{RM}) cell-like features for chimeric antigen receptor (CAR) T cell therapies, particularly for solid tumours where conventional CAR T cells often fail. T_{RM} cells possess strong tissue-homing properties, enhanced tumour retention and a distinct metabolic profile supporting survival and antitumour function. CXCR, CXC-chemokine receptor; GPC3, glypican 3; OXPHOS, oxidative phosphorylation.

Box 2 | Technological and methodological advances to improve the understanding of hepatic CD8$^+$ T$_{RM}$ cell function

- Accurate quantification of hepatic CD8$^+$ tissue-resident memory T (T$_{RM}$) cells: classical tissue extraction methods result in the selective loss of T$_{RM}$ cells, leading to underestimation of their true numbers[60].
- Improved cellular characterization: moving beyond flow cytometry, which is limited by marker selection, to more comprehensive and unbiased analytical approaches.
- Identification of distinct CD8$^+$ T$_{RM}$ cell states: surface marker expression alone often fails to accurately reflect the functional state of CD8$^+$ T cells. Advanced profiling methods such as matrix-assisted laser desorption and ionization imaging can shed more light on the functional state of hepatic T$_{RM}$ cells.
- Correlation of the CD8$^+$ T$_{RM}$ cell phenotype with function: understanding the environmental cues that tip the balance of T$_{RM}$ cells towards pathogenicity will help to precisely identify T$_{RM}$ cells in tissues that contribute to fibrosis, autoimmunity or immunity against pathogens.
- Spatial resolution of CD8$^+$ T$_{RM}$ cell interactions: mapping hepatic T$_{RM}$ cells in steady-state and inflammatory conditions will reveal critical interactions with immune and non-immune cells, shedding light on their dynamic roles in liver immunity.
- Integration of big data and machine learning: generating large-scale datasets to develop predictive algorithms for immune responses and disease progression in liver pathologies.

pancreatic tumour cells results in superior antitumour functionality. This enhanced response is manifested by increased local accumulation – facilitated by upregulated CD69 and CD103 expression and related transcriptional programs of residency – and elicitation of robust tumour-resistant effector function[161]. Similarly, studies exploring in vivo CAR T cells with an additional transgene for IL-15 confer better memory cell formation associated with a favourable oxidative metabolic profile[162,163]. Such IL-15–CAR T cells specific for glypican 3 (GPC3), an antigen widely expressed in HCC, but not the non-malignant liver tissue, have been tested in phase I trials[164,165] in patients with solid tumours including those with HCC[162], demonstrating increased polyfunctionality and enhanced cell migration into the tumour. This first-in-man trial included nine patients with HCC, three of whom received conventional GPC3–CAR T cells and six received IL-15-modified GPC3–CAR T cells. Of the six receiving IL-15–GPC3–CAR T cells, three individuals had a partial response, one remained stable and two progressed, whereas in those receiving conventional GPC3–CAR T cells, no patients showed a positive clinical response, two remained stable and one progressed[162]. Although not evidenced yet, it is interesting to speculate that IL-15-driven increases in CD69 expression levels, liver-homing chemokine receptors such as CXCR6 (refs. 12,37) might be, in part, responsible for the accumulation of IL-15–CAR T cells within tumours[162], but might also tip the balance in how these cells respond once within the tumour.

The substantial progress made in our understanding of how hepatic CD8$^+$ T$_{RM}$ cells adapt to the liver environment, including their defining markers, environmental mediators shaping their development and their role in liver disease pathogenesis, has led to pioneering IL-15–CAR T cell therapies against HCC. However, several key challenges remain unresolved. Owing to the limitations of the 'gold-standard' techniques in current preclinical models, such as parabiosis, tissue engrafting and intravascular labelling, very few studies have shown definitive confirmation of long-term residency in the liver. For instance, the highly vascularized nature of the liver complicates the distinction between true CD8$^+$ T$_{RM}$ and circulating cells, as comparable numbers of CD8$^+$ T cells are often detected in both intravascularly labelled and unlabelled fractions[60,166]. Similarly, a small but considerable population of liver CD8$^+$ T$_{RM}$ cells retains a capacity for tissue egress, migrating to the liver of partner parabionts[79]. Thus, liver residence is still most commonly inferred by varying putative residency-defining markers and gene signatures, meaning caution must be applied when comparing studies. As a result of these technical limitations, marked efforts have been directed towards developing innovative methodologies to identify and characterize hepatic CD8$^+$ T$_{RM}$ cells directly in situ[48,167,168]. These newly developed techniques, such as spatial transcriptomics, single-cell proteomics, and matrix-assisted laser desorption and ionization imaging, offer several key advantages as summarized in Box 2.

These technological advances will enable a more precise and comprehensive understanding of hepatic CD8$^+$ T$_{RM}$ cell biology, moving beyond current limitations to reveal their true abundance, functional diversity and spatial organization within the liver microenvironment. This comprehensive characterization will better distinguish protective from pathogenic CD8$^+$ T$_{RM}$ cells and inform targeted therapeutic strategies. In parallel, the development of more sophisticated in vitro models, such as liver-on-chip systems and liver organoids incorporating HSCs, LSECs and immune cells, and mimicking physiological environmental cues, will provide powerful tools to dissect the intricate environmental cues shaping CD8$^+$ T$_{RM}$ cell function. These models will enable researchers to crack the code of how hepatic T$_{RM}$ cells interpret, integrate and respond to the diversity of stimuli in the liver.

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Competing interests

The authors declare no competing interests.

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