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# Heterogeneity of tissue resident memory T cells

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ABSTRACT

Non-lymphoid organs, in mice and humans, contain $CD8^+$ tissue-resident memory T ($T_{RM}$) cells. They play important roles in tissue homoeostasis as well as defence against infections and cancer. $T_{RM}$ cells have common characteristics that enables their tissue residency and function. However, the wide variety of tissues, some with continually exposure to invading microbes, distinct organ structures and functions, impose tissue-specific differences on $T_{RM}$ cells. Upon tissue-entry, they need to adapt to local circumstances by modifying their transcriptional machinery, enabling interactions with the – often specialised – surrounding cells and available metabolites. Heterogeneity amongst $T_{RM}$ cells may have implications for their defence function, organ-specific autoimmunity and chronic immune disorders. Here we indicate shared and unique $T_{RM}$ cell features within different tissues to provide a better understanding of their function and discuss possible future research directions.

## 1. Introduction

Adaptive immunity is characterised by rapid recall responses of previously established antigen-specific memory cell populations. We will limit this perspective to CD8-expressing T cells, which upon antigen encounter and clonal expansion in secondary lymphoid organs (SLOs) undergo differentiation from a quiescent state to one that initiates transcriptional programmes and rapid cell division. This generates a T cell pool specific for the encountered antigen, the numbers to engage the invading pathogen, and flexibility to generate subpopulations that can acquire distinct functional properties and tissue distribution that are maintained for a long period in the form of memory T cells. The arms race between microorganisms and immune system has resulted in layers of immune protection with memory CD8 T cells found in functionally distinct subsets and distributed over different tissue compartments.

Memory T cells can be classified into three main populations; circulating central memory T cells ($T_{CM}$) and effector memory T cells ($T_{EM}$), as well as tissue-resident T cells ($T_{RM}$). $T_{CM}$ cells are long-lived memory cells that recirculate through the lymphatic system and blood. This is enabled by their expression of the lymphoid tissue-homing receptors CD62L and chemokine receptor (CCR)−7. $T_{EM}$ cells primarily recirculate between the blood and non-lymphoid tissues, and they do not express CD62L or CCR7 [1]. $T_{RM}$ cells remain in non-lymphoid tissue sites of intestine, skin and lung but also in non-barrier tissues such as the liver, brain and the joints. They do not recirculate through the blood as $T_{EM}$ and $T_{CM}$, and do not express CD62L or CCR7. $T_{RM}$ cells are transcriptionally, phenotypically and functionally distinct from other circulating T cell subsets. In recent years, $T_{RM}$ cells have drawn attention due to their positioning, especially in barrier tissues where they play an important role in immune surveillance against invading pathogens. Furthermore, establishment of $T_{RM}$ cells or their aberrant activation, including upon immunotherapy, is implicated in chronic disorders such as inflammatory bowel disease and vitiligo [2].

Importantly, $T_{RM}$ cells can take on tissue-specific characteristics, resulting in differential expression of proteins between similar cells in different tissues that may cause confusion over their identity as $T_{RM}$

*Abbreviations:* $T_{CM}$, Central Memory T cells; $T_{EM}$, Effector Memory T cells; $T_{RM}$, Tissue Resident Memory T cells; SLO, Secondary Lymphoid Organs; CCR, chemokine receptor.

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cells. Defining surface markers and transcription factors that discriminate $T_{RM}$ cells from other T cell subsets in mouse and human tissues remains an ongoing challenge. In this perspective, we will highlight common features of mouse and human $T_{RM}$ cells and highlight some unresolved questions.

## 2. Common features of $T_{rm}$

Although $T_{RM}$ cells share many aspects with $T_{CM}$ and $T_{EM}$ cells, they possess unique tissue residency-promoting features, some specific to their host tissue, which promote long-term retention and survival at those different sites [3, 4]. To distinguish $T_{RM}$ cells from other T cell subsets, both in mice and humans, identification via markers such as CD69, CD103, CD49a, and CD44 have extensively been explored. The field is not in agreement if all of these surface molecules are critical to identify $T_{RM}$ cells or if they are expressed simultaneously, continually or depending on the activation status. The use of so called "*in vivo* staining" is a snapshot in time providing an indication of the location of the cells during the short time, generally minutes, of antibody labelling. Parabiosis in mice remains the gold standard to determine tissue residency, but is time consuming and technically more challenging. The exact functions of several markers used to identify $T_{RM}$ cells remain incompletely understood. Although mouse models may not completely recapitulate the findings in human studies, the extent to which these differences affect the characterisation and function of $T_{RM}$ cells is still incompletely understood [5]. In this section we will define and discuss common surface markers and transcription factors that relate to most tissue resident T cells in mice and humans (Fig. 1).

In common with all antigen-experienced T cells in C57BL/6 mice, $T_{RM}$ cells express high levels of CD44. CD44 is a murine memory T cell marker and a well-characterized receptor for hyaluronic acid – an essential component of extracellular matrix and connective tissue. CD44 furthermore interacts with cell-surface glycoproteins, expressed on various cell types such as other leukocytes and epithelial cells, as such, it is involved in cell-cell interactions, cell adhesion and migration [6]. In humans, the memory T cells can be distinguished from naive T cells by expression of distinct isoforms of the lectin-binding tyrosine phosphatase CD45. High molecular weight (CD45Rhigh) splicing variants such as CD45RA and CD54RC are lost after activation and replaced by the low molecular weight form CD45RO, with possible re-expression of CD45RA [7]. Consequently, the predominant marker of (resident) memory T cells in humans is CD45RO [8].

In mice, Killer cell lectin-like G1 (KLRG1) is expressed on $CD44^+$ effector T cells, but generally absent on both $T_{CM}$ and $T_{RM}$ cells [9]. Therefore, it is a useful marker to distinguish effector T cells and $T_{RM}$ cells in tissues during an ongoing inflammatory response [10]. In humans, expression of HLA-DR, CD38, CD25, KLRG1 are increased during T cell activation with highest expression on $T_{EM}$ cells, but generally absent on $T_{RM}$ cells [11, 12]. Of note, KLRG1 expression has been reported on some $T_{RM}$ subsets in the human intestine [13]. However, it is unclear if this marks a distinct $T_{RM}$ cells subset or a recently activated $T_{RM}$ population.

### 2.1. Factors that orchestrate $T_{rm}$ cell tissue retention and maintenance

Although there are marked differences between phenotypes of $T_{RM}$ cells in different tissues and organs, depending on activation status and host species, some surface markers and transcription factors are consistently present in both organisms and provide a "core identity" of $T_{RM}$ cells. The canonical phenotype present on human and mouse $CD8^+$ $T_{RM}$ cells is defined by the surface markers CD69 and CD103.

Historically, CD69 was one of the first molecules associated with $T_{RM}$ cell identity. An early activation marker upon T cell stimulation and capable of preventing T cell egress from the secondary lymph nodes, it is downregulated $T_{RM}$ precursors and later re-expressed upon encountering antigen in the infected peripheral tissue. Here, it is maintained on $T_{RM}$ cells long-term, even in the absence of continued antigen expression. CD69 blocks Sphingosine 1-phosphate receptor 1 (S1PR1) function by reducing its presence on the cell surface and mediating the downregulation of transcription of the *S1pr1* gene [14]. S1PR1 on the cell surface senses S1P1, directing cell movement to the higher concentrations present in the blood stream and thus mediating tissue egress [15].

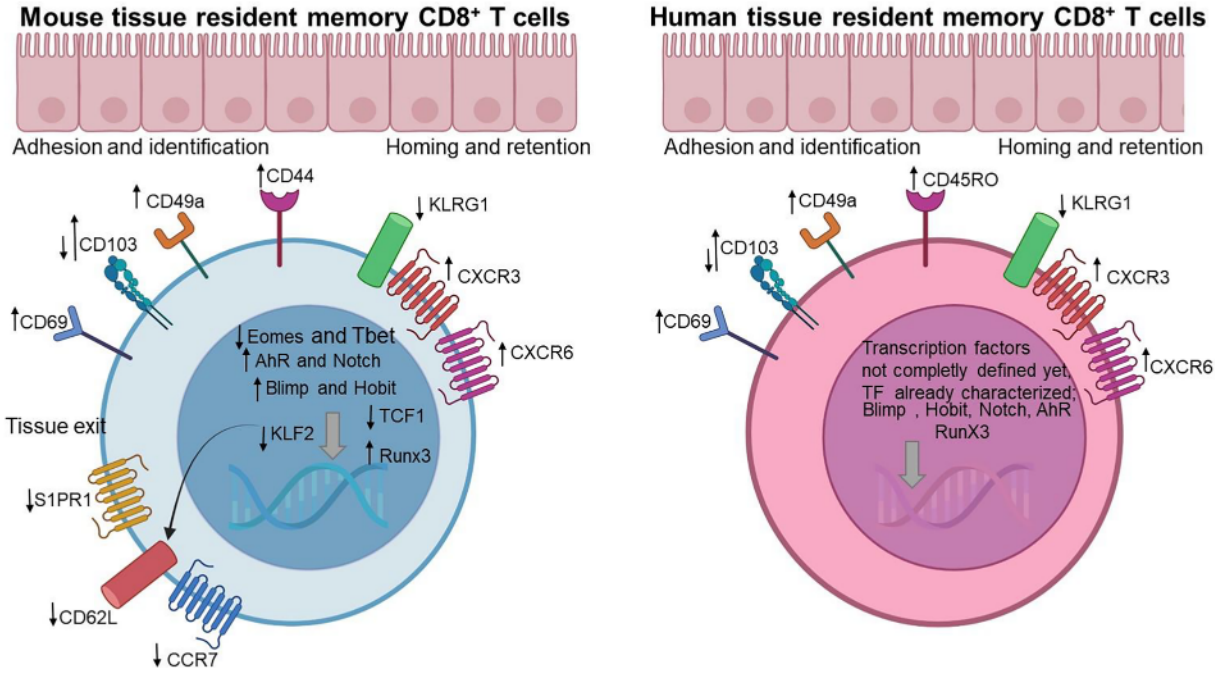


**Fig. 1.** General characterisation of TRM cells in mice and humans.Established surface markers and transcription factors in TRM cells in mice and humans. In this figure we represent surface markers and transcription factors (TF) that are characteristic for TRM cells in mice and humans identified to date. The surface markers and transcription factors that are defined can vary in expression level depending on tissue location, function and pathology condition (table 1). https://app.biorender.com/biorender-templates.

In humans, expression of CD69 on $T_{RM}$ stands in contrast to the lack of expression of other early activation markers such as CD25, CD38 and HLA-DR, which are not characteristic of $T_{RM}$ cells [5, 16].

To interact with their tissue environment and enhance retention, both murine and human $T_{RM}$ cells can express adhesion molecules such as CD103 and CD49a [17–19]. CD103 (alpha E integrin) is a component of αEβ7, a receptor for the adherent junction protein E-cadherin. In both mice and humans, $CD103^+$ $T_{RM}$ cells are particularly described in epithelial tissues, such as the skin and the intestine [9, 20], however, CD103 cannot be considered a universal marker for $T_{RM}$. Of note, *in vitro* priming of naive T cells can generate a $CD103^+$ $T_{RM}$-like phenotype [21]. Several factors, especially transforming growth factor (TGF)β, have been shown to induce CD103 expression on T cells [10, 20, 22-24]. CD103 expression is modulated via the activity of several transcription factors, including the T-box transcription factors Tbet (Tbox expressed in T cells) and Eomes (Eomesodermin) [25, 26].

CD49a, or integrin 1α, pairs with CD29 (integrin 1-β) to form very late antigen (VLA-1), which is a collagen-binding integrin. Similarly to CD103, CD49a contributes to development and/or survival of $T_{RM}$, thereby enhancing long-term persistence and regulating locomotion [19]. In mice, CD49a was found to provide resistance to active induction of apoptosis in the presence of type IV collagen and tumour necrosis factor (TNF) [27, 28]. Genetic deletion of CD49a results in a decrease of $T_{RM}$ populations and blocking CD49a with antibodies results in decline of $T_{RM}$ at mucosal sites [29, 30]. However, CD49a does not mark all $T_{RM}$ cells and may distinguish different subsets or states of activity. Interest in CD49a expression on $T_{RM}$ cells came through studies in mouse models, but human $T_{RM}$ cells share many attributes.

Lastly, most murine and human $T_{RM}$ cells express the chemokine receptor CXCR3, the expression of which is driven by Tbet [31, 32]. Although this is seen on the majority of $T_{RM}$ cells, it may be a reflection of the predominantly type 1 immune responses involving intracellular pathogens [33]. $CXCR3^-$ $T_{RM}$ cells have been observed, but these seem a rare population of cells [34]. Regardless, CXCR3 is rarely used to identify $T_{RM}$ cells.

As mentioned previously, $T_{RM}$ cells have a core transcriptional signature, which determines their differentiation and long-term survival at different tissue sites. In mice, this is characterised by reduced to absent levels of the transcription factors Kruppel-like factor 2 (KLF2) and Eomes and low expression of Tbet and T cell factor (TCF)1 compared with $T_{EM}$, $T_{CM}$ and effector cells [14, 26, 35]. Similar observations have been made for the core signature of human $T_{RM}$, which likewise display low levels of KLF2 [16], low amounts of EOMES and low to intermediat levels of Tbet [32, 36]. This characteristic TF profile reflects the altered activation status, survival and metabolic factors required for $T_{RM}$ cells to be maintained in tissues without recirculating though secondary lymphoid organs. Like $T_{EM}$ cells, $T_{RM}$ cells are characterised by the absence of lymph node homing molecules such as CD62L and CCR7, which is mediated by the downregulation of KLF2 [14]. In mice, a complex interaction between Eomes and Tbet establishes the formation of $CD103^+$ $T_{RM}$ cell [9]. Switching off Eomes expression is required for $T_{RM}$ cell development. This stands in contrast to all other known $CD8^+$T cell subsets and for reasons as yet unknown. Tbet expression is similarly reduced, however, basal levels of Tbet are required to preserve cell surface interleukin-15β-chain (CD122) expression and with it the IL-15 responsiveness [25, 26].

Additional $T_{RM}$ cell attributes are obtained with differential expression of *Znf683* (Hobit) and *Prdm1* (Blimp1) [37]. In mice, the $T_{RM}$ transcription factor Hobit is up-regulated together with Blimp1 they have a role in development of $T_{RM}$ cells and their retention in mouse epithelial tissues such as lungs, skin and intestine, by actively down-regulating the expression of CCR7, KLF2 and S1PR1 [20, 37, 38]. In humans, HOBIT and BLIMP1 are expressed in effector T cells where they correlate with expression of granzyme B [39, 40]. Hobit and Blimp1, although identified as master regulators of $T_{RM}$ in mice [20], may not be differentially expressed in human $T_{RM}$ cells relative to their expression by circulating $T_{EM}$ cells that also express HOBIT and BLIMP1 [36].

At least in mice, the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor, is crucial for the maintenance $T_{RM}$ in the skin and intestine [41, 42]. In addition to preserving $T_{RM}$ cells in epithelial tissues, it can also regulate the expression of many genes, including the cytokine IL-22 [43, 44], and cell cycle genes [20, 36, 41, 42, 45]. The role of AhR in human $T_{RM}$ cells remains to be determined, although there are indications that it may make a similar contribution to $T_{RM}$ cells as in mice [46].

In sum, many transcription factors, including Hobit, Blimp1, AhR, Tbet, and Eomes, are known mediators promoting $T_{RM}$ cell formation, with altered expression levels relative to those found in circulating memory T cells [5, 36, 47]. The transcription factors required for human $T_{RM}$ cells remain to be fully elucidated [5, 16, 36, 47]. Furthermore, the core surface receptors in both mice and humans include CD69, CD103 and CD49a – even though they cannot be considered universal markers.

## 3. $T_{RM}$ markers and retention molecules for specific tissues

T cells home to the sites of inflammation where their cognate antigen is encountered. Due to mechanisms not fully understood, $T_{RM}$ cells develop and are retained in the originally inflamed tissue for a long time. Inflammation can occur in any tissue, and these tissues provide specific functions, and are composed of different, often specialised, cell types. Hence, $T_{RM}$ cells have to adapt to the circumstances they find in the host tissue and adjust their transcriptional machinery for long-term survival. An overview is provided in Table 1.

### 3.1. Skin

Perhaps the most intensively studied population of $T_{RM}$ cells are those found in the epidermal layer of the skin. The notion of the uniformly $CD103^+CD69^+$ intra-epithelial $T_{RM}$ cells is derived from analysis of this tissue. However, more recent studies in mice have uncovered that CD103 itself is not essential for the generation or morphology of epidermal $T_{RM}$ cells, but contributes to their ability to migrate within the tissue [34]. Similar to epidermal γδ T cells, murine epidermal $T_{RM}$ cells

**Table 1**
Common markers and differences of TRM cells in different tissues, in mouse and human.

| organ | surface marker | References mouse | References human |
|---|---|---|---|
| Skin | CD69+ | [9] | [17, 48, 77, 78] |
| | CD103+ | [9] | [17, 48, 77, 78] |
| | FABP4/FABP5+ | [3, 49] | [49] |
| | CD49a+/- | [79, 80] | [17] |
| | CCR10 | [34] | [48] |
| | CCR8 | [34] | [48] |
| | CXCR6 | [34] | [48] |
| | CXCR3 | [9, 34] | [48] |
| Gut | CD69+ | [10] | [13, 54] |
| | CD103+/- | [10] | [13, 54] |
| | KLRG1+/- | | [13] |
| | CD161(int) | | [54] |
| Lung | CD69+ | [59, 81] | [36, 82] |
| | CD103+/- | [59, 81] | [36, 82] |
| | CD49a+/- | [59, 81] | [82] |
| | CXCR6 | [59] | [59] |
| | CXCR3 | [59] | |
| Exocrine Glands | CD69+ | [60, 80] | [83] |
| | CD103+/- | [60, 80] | [83] |
| | CD49a+/- | [80] | |
| | CXCR3 | [84] | |
| Liver | CD69 | [66, 80] | [64] |
| | CD103+/- | | |
| | [66, 80] | [64] | |
| | CXCR6 | [66] | [64] |
| | CXCR3 | [66] | |
| | CD49a | [85] | |

display a dendritic-like morphology and migrate at a relatively low migration speed of 1–2 μm/min [45]. In mouse models, the chemokine receptors CCR10 and CCR8 promote the recruitment of $T_{RM}$ precursors to the skin, while CXCR6 appears to be required for maintenance of normal numbers of epidermal $T_{RM}$ cells [34]. Similarly, in human skin, CCR8 expression identifies a subset of $CD8^+$ memory T cells with $T_{RM}$-like characteristics such as concomitant CD69, CXCR6 and CD103 expression [48]. The ethology of epidermal $T_{RM}$ cells has been extensively studied in mouse models, and requires the expression of CXCR3 on $T_{RM}$ precursors for efficient recruitment into the epidermal epithelium [34]. However, CXCR3 expression appeared negligible for epidermal $T_{RM}$ migration and morphology [34]. Furthermore, both human and murine skin $T_{RM}$ express fatty acid binding proteins (FABP), which promote $T_{RM}$ cell survival by mediating fatty acid uptake [49]. In mice, the expression of FABP isoforms was found to be organ specific amongst $T_{RM}$, with FABP4 and FABP5 being specific to skin $T_{RM}$ and lacking on intestinal or liver derived $T_{RM}$ [3]. Of note, it has been proposed that the integrin CD49a may be an indicator of skin $T_{RM}$ cell polarization, as in human skin from psoriasis patients $CD49a^-$ $T_{RM}$ cells produced IL-17, while $CD49a^+$ $T_{RM}$ expressed IFNγ [17].

### 3.2. Gut

The gut is the barrier organ with the largest interface to the environment. Similar to the skin, its tissue architecture consists of an epithelial layer with underlying supporting tissue (lamina propria). Both tissue compartments host populations of leukocytes (intraepithelial lymphocytes [IEL] and lamina propria leukocytes [LPL], respectively), which include $T_{RM}$ cells. Although skin IELs may rely on fatty acids, the metabolism of intestinal IELs is differently wired and appears more dependant on using sugars for their motility and scanning epithelial cells as well as primary energy source for their immune function [50–52]. While it has been reported that IEL are dominated by $CD103^+$ expression, $CD103^+$ $T_{RM}$ cells are not exclusive to the epithelial compartment and - at least in humans - are located also in the lamina propria [10, 13]. Like in other tissues CD69 is a core maker for both human and murine intestinal $T_{RM}$ cells [10, 13]. In contrast to the epidermal skin, the intestine also hosts significant compartments of $CD103^-$ $T_{RM}$ cells, which have been described in both mice and human intestinal transplant grafts [13, 53]. Their role and maintenance remains unclear, since without recent activation few if any $CD103^-$ $T_{RM}$ cells are present.

In $CD103^+CD69^+$ memory T cells in human colon were further described to express an intermediate level of the C-type lectin-like receptor CD161, which is conventionally associated with mucosal-associated invariant T cells (MAIT) and may represent a gut specific $T_{RM}$ cell marker [13, 54]. However, colon $T_{RM}$ cells display other non-conventional features of $T_{RM}$ cells such as high expression of EOMES and Tbet, but do express the chemokine receptor CXCR6 [54].

Homing of intraepithelial $T_{RM}$ cells is partly chemokine mediated, as the deletion CCL25 or its receptor CCR9 in mice results in reduction of IELs [55, 56], which was attributed to impaired ability of these T cells to localize to the gut wall. Homing of intestinal $T_{RM}$ is furthermore mediated by the integrin $\alpha_4\beta_7$, which mediates both rolling and solid adhesion of $CD8^+$ T cells in the mucosa. This was exemplified in patients with Crohn disease, where etrolizumab (anti-β7) resulted in reduced homing of $CD8^+$ cytotoxic T cells to the intestine [57].

### 3.3. Lungs

In contrast to skin and gut, lung lack the layered structure of epithelial and sub-epithelial tissues, and instead are organised as a branching network of bronchial and alveolar ducts ending in alveoli. The transcriptional signature of $CD103^+$ human lung derived T cells overlapped significantly with the signature of dermis derived $CD103^+$ T cells, indicating that a core $T_{RM}$ cell signature is consistent in both tissues [58]. Others have proposed that $CD103^-$ $T_{RM}$ are also present in the human lung, as these subsets transcriptionally resemble $CD103^+$ $T_{RM}$ cells more closely than circulatory memory T cells [36]. Human lung $T_{RM}$ cells displayed expression of CD49a and CXCR6 [58] and elevated levels of CXCR3, CCR5 and CCR6 compared to circulatory memory T cells [36]. CXCR6 was demonstrated to mediate localization to the airway in mice [59]. Similar to other $T_{RM}$ subsets human lung $T_{RM}$ cells are characterised by low expression of EOMES and Tbet [36]. $T_{RM}$ in the lungs have a role in maintaining tissue homoeostasis, recent publication are also showing human lung $T_{RM}$ have a potential in anti-tumour immunity and immune surveillance and a role in immunopathology in chronic airway inflammation [47].

### 3.4. Exocrine glands

Exocrine glands such as salivary and lacrimal glands present a particular challenge for immune-surveillance. The structure of their tissue architecture resembles the lung, starting with bulbous agglomerates of secretory cells (acini) that lead into branching secretory ducts. Thus, they present a single layer of epithelium which is interspersed with non-epithelial stroma. Consequently, exocrine glands harbour both intra- and extra-epithelial $T_{RM}$. It has been proposed that CD103 expression can be used to distinguish both populations in mice [60], however, other work has indicated that murine exocrine gland $T_{RM}$ cells may freely cross between epithelial and stromal compartments [61]. Similar to other $T_{RM}$ subsets, murine salivary gland $T_{RM}$ cell express CXCR3, which is not required for their homoeostatic migration, but may aid to position $T_{RM}$ to the vicinity of local inflammation [61].

### 3.5. Liver

Unlike the previously discussed organs the liver is not a barrier tissue. It receives a dual blood supply from the portal artery and the portal vein, which carries blood rich in nutrients and potential antigens from the intestinal tract. Both vessels pool into the liver capillaries called sinusoids, where blood flow is slow and blood derived molecules and cells can come into direct contact with hepatocytes via the fenestrated sinusoidal epithelium [62].

CD69 has been established as the most important - despite imperfect - marker for residency in liver memory T cells in both mice and humans [63, 64]. Another key marker for liver $T_{RM}$ is CXCR6, which is negligible for recruitment of memory T cells to the liver, but mediates maintenance of the intrahepatic memory T cell pool in mice [65]. In contrast to intraepithelial $T_{RM}$ subsets in other organs, liver $T_{RM}$ generally lack CD103 in mice [66], while at least some human liver $T_{RM}$ express CD103 [67]. This is in line with another particularity of intrahepatic $T_{RM}$: unlike in any other tissue, liver $T_{RM}$ reside not within the stromal epithelium but within the microvasculature of the liver. In mice, intravascular crawling was shown to be mediated by interactions of the LFA-1 integrin with its ligand ICAM1, which is constitutively expressed on liver sinusoidal epithelial cells [68]. Presumably, intrahepatic $T_{RM}$ perform immune surveillance of hepatocytes by extending protrusions through the fenestrated sinusoidal endothelium, a mechanism that was previously described for murine CD8+ effector T cells [69].

Murine liver $T_{RM}$ were found to express increased levels of CXCR3 [66], however, CXCR3 was not required for the formation of CD8 T cell memory in the liver in mouse model of malaria infection [65]. Also human intrahepatic $T_{RM}$ express CXCR3, as evidenced by the high expression of CXCR3 on liver $T_{RM}$ which persisted in human allografts for over a decade [67].

## 4. Future directions

$T_{RM}$ cells where first characterised more than a decade ago, as a subset of memory T cells that do not recirculate. Important questions are awaiting to be answered, which will give new impulse for the treatment and diagnosis of diseases with $T_{RM}$ cell involvement, such as tissue-

specific autoimmunity and cancer. Studying T cells in the tissue changed the way tissue T cell immunity in mice is analysed but poses challenges in studying $T_{RM}$ cells in humans, requiring the implementation of more invasive tissue sampling methods.

It has long been an open secret that isolated $T_{RM}$ cells grossly underrepresent the true number of $T_{RM}$ cells present *in situ* and it remains unclear to which extent the fraction of $T_{RM}$ cell amenable to isolation represent the total population [63]. Cell death during $T_{RM}$ cell isolation has partially been attributed to activation induced cell death mediated by P2RX7 ion channels, a pathway which can be blocked in mice by *in vivo* application of ARTC2.2 blocking nanobodies [70, 71]. However, it is likely that additional pathways of cell death or damage exist. Furthermore, no equivalent protective agent has been found in the preparation of human samples. Perhaps the advancement of tissue section based technologies such as spatial transcriptomics, highly-multiplexed immunofluorescent imaging and mass cytometry imaging will ultimately provide means to characterise the true population of $T_{RM}$ cells. We highlight four areas in which progress is both predicted and focus needed, to exploit our evolving knowledge of $T_{RM}$ cell biology in therapeutic settings such as organ-specific chronic immune disorders and autoimmunity as well as cancer therapy.

### 4.1. Identification

To date, long-term tissue residency is the sole true defining characteristic of $T_{RM}$ cells. However, this can only be directly determined with a limited set of techniques, such as parabiosis in mice or organ transplantation in humans. Such in depth studies of resident T cell populations from human organ transplants have revealed a surprising heterogeneity in $T_{RM}$, while failing to reveal any universal $T_{RM}$ markers. Consequently, any experimental setup that relies on a limited set of markers to identify $T_{RM}$ (instead of truly using tissue residency as determining factor) is at best biased. As cell markers will likely remain a crucially important tool for the foreseeable future, the field maybe required to move away from a descriptive label "tissue-resident" memory T cell and instead adopt a more function-orientated perspective of the "tissue-interacting" memory T cell. Some of this will be based on surface markers, indicating activation state and functional capacity, as well as transcriptional profiling, identifying progeny and functional capability. Also here, multiplexed immunofluorescent imaging, used of indicator dyes for metabolic activity, and mass cytometry imaging, focused on metabolites and metabolic pathways will need to be developed and optimised.

### 4.2. Diversity

Diversity is key to a successful immune defence, with heterogeneity an important aspect to success. $T_{RM}$ cells are part of the heterogeneity and as a population are heterogeneous themselves between different tissues, reflecting different organ structures and function. Despite technical challenges of obtaining all tissue resident T cells, there is already and abundance of single cell RNA sequencing studies highlighting the diversity of $T_{RM}$ subsets between different organs, within the same organ, and under different pathological conditions [13, 58, 72-75]. Given this diversity, nomenclature may have to evolve to not simply speak of "$T_{RM}$" but to include further qualifying features regarding activation and functional status, progenitor potential, polarization and ontogeny. Focus has been on the $CD8^+$ $T_{RM}$ cell population, but diversity and plasticity is expected to be larger in the $CD4^+$ T cell population with physiological effects on local immune cells as well as tissue stroma cells.

With research of $T_{RM}$ cell heterogeneity, especially with the use of multi-omics methods of $T_{RM}$ cells in healthy and in pathological conditions such as autoimmunity and cancer, may open new opportunity for therapeutics, precisions medicine and diagnostic approaches. Furthermore, $T_{RM}$ cell biology and functional knowledge could be exploited in anti-tumour therapies.

### 4.3. Maintenance

$T_{RM}$ cells possess many phenotypical and molecular properties, such as downregulation of tissue egress-related genes and the upregulation of genes regulating tissue interactions, which largely maintains the cells in the target tissues. However, all T cells rely on cell-cell interactions, survival factors, such as IL-7 and IL-15 and available metabolites. It is not fully understood how $T_{RM}$ cells, that show high motility [45, 50], obtain their metabolites, especially in highly metabolic active organs, that enable long-term survival and self-renewal in the tissues. Furthermore, the underlying biochemical mechanisms that maintain their semi-activation status remain largely unexplored, but may actually include relevant therapeutic targets. Part of the technical hurdle is obtaining high quality tissue-derived T cells of high purity that need to be assessed outside of their physiological environment and cannot be *in vitro* interrogated for more than a few hours due to their constant need for interactions with tissue cells for their survival [76]. Three-dimensional culture systems may overcome part of this shortcoming, but are composed of mixed cell lineages and are not easy to scale up.

### 4.4. Whole tissue immunology

The increasing recognition of the importance and abundance of $T_{RM}$ cells has opened the daunting field of tissue immunology. For future research on $T_{RM}$ it will likely become mandatory to explore the bidirectional interplay between $T_{RM}$ and their surroundings in health and disease, including interactions with immune, stromal and neuronal cells, extracellular matrix, soluble factors, and tissue factors and metabolic status such as pH and oxygen levels. These kind of analyses will be especially interesting and challenging in the context of chronic inflammatory conditions such as autoimmunity, chronic infections and cancer, offering opportunities for new therapeutic targets and treatments.

## Declaration of Competing Interest

M.I. participates in advisory boards/consultancies for Gilead Sciences, Roche, Third Rock Ventures, Amgen, Allovir, Asher Bio, ENYO Pharma, Antios Therapeutics.

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