Journal for ImmunoTherapy of Cancer

Tissue-resident memory T cells in gastrointestinal cancer immunology and immunotherapy: ready for prime time?

Syrine Abdeljaoued,[1,2] Sara Arfa,[1,3] Marie Kroemer,[1,2,4] Myriam Ben Khelil,[1] Angélique Vienot,[1,5] Bruno Heyd,[3] Romain Loyon,[1] Alexandre Doussot,[3] Christophe Borg[1,2,5]

To cite: Abdeljaoued S, Arfa S, Kroemer M, *et al*. Tissue-resident memory T cells in gastrointestinal cancer immunology and immunotherapy: ready for prime time? *Journal for ImmunoTherapy of Cancer* 2022;**10**:e003472. doi:10.1136/jitc-2021-003472

Accepted 28 March 2022

[1]RIGHT Interactions Greffon-Hôte-Tumeur/Ingénierie Cellulaire et Génique, University of Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Besançon, France
[2]Clinical Investigational Center, CIC-1431, Besançon, France
[3]Department of Digestive and Oncologic Surgery, Liver Transplantation Unit, University Hospital of Besançon, Besançon, France
[4]Department of Pharmacy, University Hospital of Besançon, Besançon, France
[5]Department of Medical Oncology, University Hospital of Besançon, Besançon, France

Correspondence to
Dr Syrine Abdeljaoued; abdeljaoued.syrine@hotmail.fr

ABSTRACT

Tissue-resident memory T (T_{RM}) cells have emerged as immune sentinels that patrol the tissue microenvironment and orchestrate localized antitumor immunity in various solid cancers. Recent studies have revealed that T_{RM} cells are key players in cancer immunosurveillance, and their involvement has been linked to favorable responses to immunotherapy as well as general better clinical outcome in cancer patients. In this review, we provide an overview of the major advances and recent findings regarding T_{RM} cells phenotype, transcriptional and epigenetic regulation in cancer with a special focus on gastrointestinal tumors. Finally, we highlight the exciting clinical implication of T_{RM} cells in these types of tumors.

INTRODUCTION

The tumor microenvironment (TME) represents a complex and dynamic structure with several actors from tumor-fighting cells such as cytotoxic $CD8^+$T cells, T helper 1 (TH1) cells to immunosuppressive ones such as regulatory T cells (Treg), myeloid-derived suppressive cells, tumor-associated macrophages to cancer-associated fibroblasts.[1] The Composition of the TME dictates not only the patient's prognosis but also treatment response. Based on the immune contexture of the TME, cancers are now classified into two major groups: 'cold' tumors (with low to absent T cells infiltration) and 'hot' tumors (with high T cell infiltration).[2] Gastrointestinal (GI) cancers are one of the most prevalent and death-leading cancers followed by lung and breast cancers (BC). The majority of GI tumors are essentially classified as cold tumors with the minor exception of tumors with microsatellite instability (MSI). Understanding the interplay between the immune system and the tumor cells has helped tremendously better cancer stratification as well as therapeutic decisions for each patient. An important proof of concept observation in highlighting the key role of the immune infiltrates in the control of tumor, is the positive correlation between tumor-infiltrating lymphocytes (TILs) levels and cancer prognosis observed in a large spectrum of solid cancers including GI tumors. One example is the tremendous success of the 'immunoscore' in colon cancer treatment. Based on $CD3^+$ and $CD8^+$ T cells density in the tumor, Galon *et al* were able to outline the immune fitness of a given tumor, to better stratify patients according to their prognosis, and to predict their response to therapies.[3 4] Remarkably, the immunoscore exceeded MSI status in predicting patients' survival and disease recurrence.[5] Taking together, these observations highlight the key role played by the immune system in shaping cancer progression, and suggest that a comprehensive characterization of the composition of the immune infiltrate in GI cancers is evergrowingly advocated, and is crucial for better treatment decision making.

Maintaining a memory from a previously encountered antigen is one of the most fundamental features of the immune system. On encountering their cognate antigen, naive T cells go through clonal expansion and become effector T cells. Subsequently, these cells undergo a bifurcation in their differentiation leading to the generation of a major subset of short-lived terminally differentiated effector T cells and a minor subset of memory T cell precursors. Generally, memory T cells are subdivided into two major subpopulations: central memory T cells (T_{CM}) and effector memory T cells (T_{EM}). Classification of these subsets relies on the expression levels of the lymphoid homing molecules CD62L and CCR7.[6] While T_{CM} express both CD62L and CCR7, T_{EM} on the other hand express neither of these markers. Lately, a novel subpopulation of memory T cells named 'Tissue-resident memory T cells' (T_{RM}) has been described. In contrary to T_{CM}

and T_{EM} that are mainly found recirculating between the blood and peripheral tissues; T_{RM} cells persist in peripheral tissues.[7 8]

T_{RM} cells can induce potent imminent localized immune responses against diverse pathogens. In the central nervous system (CNS), peripheral immunizations led to the generation of robust T_{RM} cells conferring long-term protection against CNS infection.[9] Additionally, in the brain during a secondary challenge, T_{RM} cells autonomously cleared lymphocytic choriomeningitis virus (LCMV) independently of the presence of circulating memory T cells.[10] Along with mouse models, T_{RM} cells specific to a wide spectrum of viruses such as CMV, hepatitis B virus (HBV), Epstein-Barr virus, and HIV were also detected in diverse human tissues.[11–15] Such findings identify T_{RM} cells as a potent, first-line, self-sufficient adaptive immune response in non-lymphoid tissues.

T_{RM} cells have been reported in several human tissues such as the pancreas, liver, intestine, skin, kidney, brain, lung, as well as lymph nodes, adipose tissues, and salivary glands.[16–26] Various studies reported a core transcriptional residency program of T_{RM} cells characterized by high expression of adhesion and retention biomarkers as well as down-regulation of tissue egress ones (S1PR1, CCR7, CD62L).[23 27] Expression of CD103 and/or CD69 are considered bona fide markers of T_{RM} cells. CD103 is essentially restricted to $CD8^+$ T_{RM} cells, with little expression on $CD4^+$ T_{RM} cells. CD103 or Integrin α_E pairs with integrin β_7 to form a heterodimeric receptor that binds to E-cadherin and enables tissue retention of CD103-expressing T cells.[28 29] Similarly, CD69, a type II C-lectin counteracts tissue egress by down-regulating the expression of sphingosine-1-phosphate receptor-1 (S1PR1).[30 31] Consequently, the expression of these biomarkers by T_{RM} cells sustains their peripheral tissue retention. Furthermore, a recent study conducted on over 50 000 activated and resting human T cells from lung, lymph nodes, bone marrow, and blood revealed that both resting and activated $CD4^+$ and $CD8^+$ T_{RM} expressed the canonical biomarkers CXCR6 and CD49a.[32] CXCR6 is a chemokine that promotes extra-lymphoid tissue homing for lymphocytes and was reported to regulate T_{RM} cells' localization to the airways.[33] CD49a (also known as Integrin α_1 subunit) pairs with integrin β_7 to constitute VLA-1 (Very Late Antigen 1) which binds to collagen IV.[34 35] CD49a was described as a regulator of cutaneous T_{RM} cells persistence and is a biomarker for highly cytotoxic T_{RM} cells.[36 37] This T_{RM} signature was largely enriched in lung tissue followed by the lymphoid site.[38] Interestingly, although T_{RM} cells are defined as memory T cells expressing tissue residency biomarkers, these cells display phenotypic as well as functional tissue-specific heterogeneity dictated by the tissue environment, which will be discussed in detail later in this review.

One of the major limitations in studying T_{RM} cells in human tissues is the exclusive use of the phenotypic characterization for T_{RM} cells identification, which reliability is highly questioned as certain of the tissue residency markers mentioned above (eg, CD69, CD49a) could also be expressed by circulating T cells. Results from solid-organ transplantation and antibody-depletion studies allowed the identification of human T_{RM} cells based on their functional characteristics. In a study conducted on patients who had received pancreatic-duodenal transplantation (Tx), Zuber *et al* reported the presence of donor CD8 T cells for more than 600 days in some non-rejected transplants.[39] In parallel, by studying normal and transplanted human small intestine (SI), Bartolomé-Casado *et al* demonstrated that the majority of both intraepithelial (IE) and lamina propria (LP) T cells were tissue-resident and persisted over a year in the graft.[40] Interestingly, the IE and LP T_{RM} cells were phenotypically, clonally, and functionally distinct, with LP $CD8^+$ T_{RM} cells exhibiting higher polyfunctionality and more potent cytokine production (GZMB, perforin) (table 1). Another study showed that the use of low-dose alemtuzumab, an anti-CD52 antibody that depletes circulating blood T cells and effectively treated patients with leukemic cutaneous T cell lymphoma, induced depletion of T_{CM} cells but sessile, non-circulating skin T_{EM} cells were spared and showed higher IFN-γ production.[41] Additionally, alemtuzumab-treated patients presented lower marked infections despite the total absence of circulating T cells. These observations provided evidence of the existence of non-recirculating skin resident T cells, that are capable of providing front-line protection against infection even in the absence of circulating T cells recruitment.

Most of our understanding of T_{RM} cell biology stems from studies conducted on T_{RM} cells discovered in healthy tissues. Understanding the underlying mechanisms of T_{RM} cells' differentiation, maintenance, and function in the context of cancer is an ongoing process. Here, we provide an overview of major advances and recent findings regarding T_{RM} cells phenotype, transcriptional and epigenetic regulation in cancer with a special focus on GI tumors. Finally, we highlight the exciting clinical implication of T_{RM} cells in these cancers.

HALLMARK FEATURES OF T_{RM} CELLS IN THE GI TRACT

T_{RM} cells' presence was described in a wide range of GI tissues.[16 42–45] In the intestine, T_{RM} cells have been widely studied in mice and were reported to be essentially lodged in the IE niches, expressing CD103 and CD69.[46–49] Recently, single-cell RNA sequencing (scRNAseq) analyses identified distinct intestinal antigen-specific T_{RM} cells subsets based on the expression of transcription factors (TF) Blimp1 and Id3 at different memory time points post LCMV infection.[50] These subsets shared transcriptional features of effector like T_{EM} cells and T_{CM} cells and they strikingly presented inter and intratemporal heterogeneity. While $Id3^{low}$ $Blimp1^{high}$ cells were present at high levels early after LCMV infection, the frequency of $Id3^{high}$ $Blimp1^{low}$ cells increased by 10-fold during the course of LCMV infection and was associated with an enriched memory gene expression signature.

Table 1 Phenotypic and functional heterogeneity of T_{RM} cells across organs

Localization		Phenotype	Functional characteristics	Reference
CD8 T_{RM}				
Gut	mice	$Id3^{low}$ $Blimp1^{high}$ $Id3^{high}$ $Blimp1^{low}$		50
	Human	$CD103^+CD69^+$	Highly polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$)	51
		$\beta2integrin^+CD103^-CD69^+$	Highly cytotoxic ($GZMB^+$)	
	IE	$CD103^+$ $KLRG1^-$ $CD28^{low}$ $2B4^{high}$ $CD161^{high}$ $CD127^{high}$ $PD\text{-}1^{low}$	Damped polyfunctionality Damped cytotoxicity	40
	LP	$CD103^+$ $KLRG1^-$ $CD28^{low}$ $2B4^{high}$ $CD161^{high}$ $CD127^{high}$ $PD\text{-}1^{low}$	Highly polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$) $GZMB^+$, $Perforin^+$	
		$CD103^-$ $KLRG1^-$ $CD28^{high}$ $CD161^{low}$ $CD127^{low}$ $PD\text{-}1^{high}$ $NKG2D^{high}$	Polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$)	
		$CD103^-$ $KLRG1^+$ $CD28^{high}$ $CD161^{low}$ $CD127^{low}$ $PD\text{-}1^{high}$ $NKG2D^{high}$	Highly cytotoxic ($GZMB^+$, $Perforin^+$)	
Liver	mice	$CD69^+$ $CD103^-$	Highly polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$)	55
	Human	$CD69^+CD103^+$ $CXCR6^+$ $CXCR3^+$	High IL-2 production	11
Pancreas	Human	$CD69^+$ $CD103^+$ $CD49a^+$ $CD101^+$ $PD\text{-}1^+$	$GZMB^+$ Highly polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+$)	16
Skin	mice	$CD69^+$ $CD103^+$	Damped polyfunctionality ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$)	55
		$CD69^+$ $CD103^+$ $CD49a^+$	Increased IFN-γ production	37
Salivary gland	mice	$CD69^+$ $CD103^-$ $CD69^+$ $CD103^+$	Highly polyfunctional ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$) Damped polyfunctionality ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$)	55
Lymph nodes	human	$CD69^+$ $CD103^-$	$IFN\text{-}\gamma^+$, $IL\text{-}2^+$	16
CD4 T_{RM}				
Liver	human	$CD69^{high}$ $CXCR6^+$ $CD49a^+$ $PD\text{-}1^+$ $S1PR1^-$ $CD69^{int}$ $CXCR3^+$ $CX3CR1^+$ $CXCR1^+$	TH1 cytokine production (IL-2, IFN-γ, IL-21) TH2 cytokine production (IL-4)	56
Small intestine	human	$CD69^+$ $CD103^+$ $2B4^+$ $CD49a^+$ $CXCR6^+$ $CD101^+$ $CD161^+$ $CD28^{low}$ $CD69^+$ $CD103^-$ $KLRG1^+$ $CD49a^+$ $CXCR6^+$ $CD101^+$ $CD161^+$ $CD28^{low}$	TH1 cytokine production ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$) $GZMB^+$, $Perforin^+$, $IL\text{-}17^+$ TH1 cytokine production ($IFN\text{-}\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$) $Perforin^+$	57

IE, Intra-epithelial; LP, lamina propria.

In addition, the $Id3^{high}$ cell subset had a more long-lived transcriptional profile and expressed higher levels of CD69 corresponding to a T_{RM} phenotype, suggesting that this $Id3^{high}$ $Blimp1^{low}$ cell subset represents T_{RM} cells or T_{RM} precursors. In contrast, in the human SI, T_{RM} cells represented the majority of $CD8^+$ T cells accumulated in both the LP and the epithelium, expressing CD103 and CD69 and demarcated by long-term persistence and polyfunctionality ($IFN\text{-}\gamma^+$ $IL\text{-}2^+TNF\text{-}\alpha^+$).[40] Using scRNAseq, Fitz Patrick *et al* recently identified two major $CD8^+$ human intestinal T_{RM} subsets with distinct phenotypic and functional features; $CD103^+CD69^+$ T_{RM} cells and $\beta2\text{-integrin}^+CD103^-CD69^+$ T_{RM} cells; $CD103^+CD69^+$ T_{RM} displayed greater polyfunctionality, whereas $\beta2\text{-integrin}^+CD103^-CD69^+$ T_{RM} cells had higher granzyme expression.[51]

In the liver, T_{RM} cells patrol the hepatic sinusoids, which allow them to interact with a vast variety of circulating cells and antigens.[52] Contrarily to gut T_{RM} cells, liver T_{RM} were essentially identified as $CD69^+$ cells lacking CD103 expression. Liver T_{RM} do not require CD103 for tissue adhesion but rather LFA-1 expression.[53] However, a small subset of liver T_{RM} cells was identified as $CD69^+CD103^+CXCR6^+CXCR3^+$ cells poised for non-cytolytic antiviral effector functions.[11 54] In line with the observed

heterogeneity in the intestine, a novel study revealed that liver and skin T_{RM} illustrate two extremes of phenotypic variations.[55] While liver T_{RM} were essentially $CD103^-$ $CD69^+$, skin T_{RM} were exclusively $CD103^+$ $CD69^+$ cells exhibiting high PD-1 expression. Strikingly, this observed phenotypic variation was associated with a functional heterogeneity mirrored by high polyfunctionality and an increased proliferative potential of liver T_{RM} cells, while skin T_{RM} were less polyfunctional but with higher longevity.[55] Interestingly, the investigation of T_{RM} cells phenotype and function in the salivary glands revealed the presence of two T_{RM} subsets $CD103^-CD69^+$ and $CD103^+CD69^+$ endowed with the same functional characteristics as liver and skin $T_{RM,}$ respectively. Hence, the salivary gland model proved the existence of an intraorgan phenotypic as well as a functional heterogeneity of T_{RM} cells in addition to the previously discussed inter-organ variability. $CD8^+$ $CD69^+CD103^+PD\text{-}1^{high}$ T_{RM} cells were also reported in the pancreas, showing an almost exclusive lodgment in the exocrine areas.[16] Consistently with previously discussed results, pancreatic T_{RM} cells were reported to be phenotypically and functionally distinct from neighboring GI sites (jejunum) and lymphoid tissues. T_{RM} cells in the pancreas showed higher expression of PD-1 and CD49a compared with T_{RM} cells in the jejunum and pancreas-draining lymph nodes, in addition to the significantly higher expression level of GZMB.[16]

Although little is known about hepatic $CD4^+$ T_{RM} characteristics, a recent study has identified two phenotypically and functionally heterogeneous intrahepatic $CD4^+$ T_{RM} subsets according to CD69 expression.[56] $CD69^{high}$ T_{RM} cells occupied sinusoidal and periportal niches and were characterized by the expression of CXCR6, CD49a, PD-1, and the production of TH1 cytokine. $CD69^{int}$ T_{RM} cells had a distinct profile and were characterized by the expression of CX3CR1, CXCR3, and CXCR1, as well as by the production of IL-4. In transplanted duodenum in humans, CD4 $+T_{RM}$ cells also presented intraorgan heterogeneity with the vast majority of $CD4^+$ T_{RM} being $CD69^+CD103^-$, however, a small fraction expressed $CD103^+$ and was exclusively lodged in the LP.[57] Although both $CD4^+$ T_{RM} subsets displayed a TH1 cytokine profile, $CD103^+$ cells produced significantly higher levels of GZMB and contained a small fraction of T_{RM} cells that produced IL-17.

Although T_{RM} cells share a common transcriptional foundation to establish tissue residency (figure 1), recent studies gave great insight into their phenotypic heterogeneity which was completely independent of the infection model but stringently tied to their tissue of lodgment. Interestingly, whether T_{RM} are localized in the GI tract or the skin or the salivary glands, they did exhibit a phenotypic heterogeneity that conferred heterogenous functional properties to these cells (summarized in table 1).

Finally, recent findings unveiled tissue-specific metabolic requirements of T_{RM} cells. Although fatty acid-binding proteins 'FABP4' and 'FABP5' were reported to be important for skin T_{RM} cells persistence, a novel study

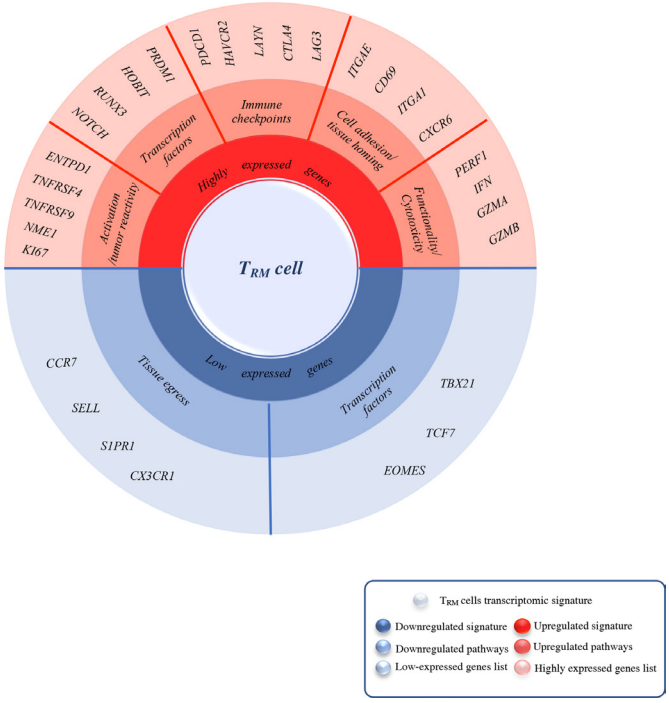

Figure 1 Summary of the most upregulated/ downregulated genes in T_{RM} cells identified by Bulk/Sc-RNA sequencing. This spin chart summarizes the core residency signature specific to T_{RM} cells compared with T_{EM} and T_{CM} identified by bulk and/or single-cell analysis. T_{RM} signature is mainly characterized by high expression of genes encoding for tissue residency and immune checkpoints (in red), both quite tissue-specific, in this figure, we also focused on those GI cancers specific such as CD103, CXCR6, PD-1, and LAG-3. Another remarkable feature of T_{RM} cells signature is the upregulated expression of cytotoxicity and functionality encoding genes compared with their memory counterparts T_{EM} and T_{CM}. Along with this upregulation, certain genes signaling are either completely shut down (in blue) such as tissue egress ones (*SELL*, *CCR7*) and TCF1 which inhibit *ITGAE* (CD103) expression or downregulated such as *TBX21* (T-bet) for IL-15R expression maintenance. GI, gastrointestinal; T_{CM}, central memory T cells; T_{EM}, effector memory T cells; T_{RM}, tissue-resident memory T cells.

by Frizzell *et al* demonstrated that the expression of FABP encoding genes in T_{RM} cells is dictated by their tissue of lodgment.[58] While skin T_{RM} cells showed high expression of *Fabp4* and *Fabp5*, T_{RM} cells lodged in the epithelium of the SI (SI-IEL) showed high expression of *Fabp1*, *Fabp2*, and *Fabp6*, whereas liver T_{RM} cells expressed high levels of *Fabp1*. Interestingly, the expression of FABP encoding genes was driven by tissue-specific mediators rather than a residency program.

T_{RM} PHENOTYPE IN GI CANCER: A FIELD OF ONGOING INVESTIGATIONS

Several independent studies reported the presence of T_{RM} cells in various cancer types including colon cancer,[44] pancreatic cancer,[42] melanoma,[59] lung cancer,[60] head and neck squamous cell carcinoma,[61] and bladder cancer

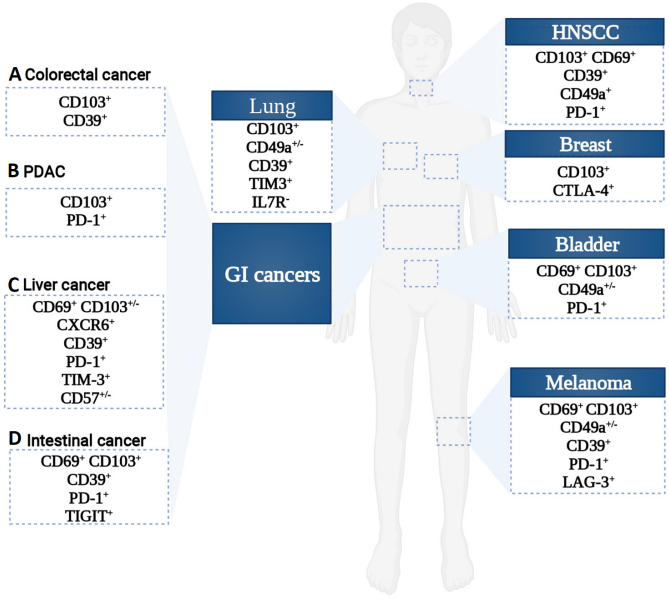

Figure 2 Phenotypic heterogeneity of CD8 T_{RM} cells across cancer types. An overview of the reported CD8 T_{RM} cells phenotype in GI and non-GI cancers showing an inter and intra-organ heterogeneity. HNSCC, head and neck squamous cell carcinomas; GI, gastrointestinal; PDAC, pancreatic ductal adenocarcinoma.

(figure 2).[62 63] Remarkably, in the majority of these studies, T_{RM} cells were reported to express the canonical tissue residency biomarkers CD103 and/or CD69. However, it is important to note that CD103 has also been reported to be a hallmark for tumor-infiltrating Treg and is expressed on dendritic cells (DCs)[64 65] and that CD69 is a well-established T cell activation marker.[31] Therefore, taken solely these biomarkers does not represent an exclusive hallmark of tissue residency. Consequently, the use of a single biomarker to identify T_{RM} cells is overly simplistic, and in-depth phenotypic and functional investigations are warranted to identify novel, more refined biomarkers for T_{RM} characterization.

Although T_{RM} cells phenotype differs between tissue sites and organs, in GI cancers, T_{RM} cells were essentially identified as $CD103^+$, notably in colorectal cancer (CRC), pancreatic cancer, gastric cancer, esophageal cancer, and hepatocellular carcinoma (HCC).[42 44 66–68] The high expression of CD103 by T_{RM} cells is possibly resulting from the epithelial origin of these cancers. A subset of $CD8^+CD103^+CD39^+$ T_{RM} has also been described in CRC.[69] Transcriptomic profiling of this subset unveiled a T_{RM} signature characterized by high expression of *HAVCR2*, *CTLA4*, and *LAYN*, while still exhibiting high expression of cytotoxic proteins (GZMA/GZMB/GZMH, TNF, Perforin 1, and IFN-γ). Luckily, the field of T_{RM} phenotyping is gaining huge momentum since the emergence of sc-RNAseq technology, which helps to deciphering the underlying heterogeneity of T_{RM} cells in the context of cancer as well as identifying novel T_{RM} subsets. A recent single-cell study conducted on T_{RM} cells in lung cancer enabled the identification of a novel uncharacterized tumor-associated antigen specific $CD8^+$ T_{RM} subset defined as $CD103^+TIM\text{-}3^+IL\text{-}7R^-$.[38] Data analysis of this T_{RM} subset, showed enrichment in transcripts encoding for high cytotoxic activity, as well as inhibitory molecules such as *CTLA4* and especially *PDCD1* transcripts. Expression of these biomarkers is known to be the most emblematic hallmark of 'T cell exhaustion', a state of functionally compromised T cells (reviewed in[70 71]). Contrarily to effector T cells, expression of these checkpoints wasn't related to an exhausted state in T_{RM}, but rather to a functionally active one.[38] In line with these observations, single-cell profiling of TILs in BC revealed a $CD8^+$ $CD103^+$ T cell subset with a core transcriptional profile of tissue residency.[72] This subset also exhibited high expression levels of immune checkpoints and presented high levels of transcripts encoding for cytotoxic molecules.

Despite the emergence of few studies investigating the transcriptional landscape of TILs in certain GI tumors such as CRC and liver cancer by single-cell sequencing, transcriptional profiling of T_{RM} cells has not been completely elucidated on a single cell level yet. Nevertheless, dimensionality reduction and clustering analysis of $CD8^+$ TILs in HBV-induced HCC revealed five $CD69^+PD\text{-}1^+$ T_{RM} subsets that could be separated according to CD103 and CD57 expression.[73] Consistently, ScRNAseq of HBV specific $CD8^+$ T cells revealed two major T_{RM} subsets coexpressing CD103 and CD69, and despite PD-1 expression, these cells do not display characteristics of exhausted T cells.[73] Strikingly, the presence of these intratumoral HBV-specific T_{RM} cells was correlated with a better prognosis of HBV-induced HCC patients, which might strongly be attributable to their role in controlling tumor growth. Taken together, these transcriptomic analyses helped to mature our understanding of the transcriptional landscape of T_{RM} cells in certain types of solid tumors as well as the identification of novel tumor-specific subsets of T_{RM} sharing the expression of residency biomarkers as well as a sustained activation, and tumor reactivity (figure 1). However, further investigations on the single-cell level of GI ones are warranted to decipher the intra-tumoral phenotypic heterogeneity of T_{RM} cells which may help to improve T_{RM} subsets identification according to tumor type.

T_{RM} CELLS DIFFERENTIATION AND MAINTENANCE

Cues promoting T_{RM} cell ontogeny and differentiation remain poorly understood. Two models explaining the generation of committed precursors for memory T cells populations including T_{RM} cells were proposed: The 'One cell, one fate' model, which speculates that naïve T cells are predetermined to give rise to either memory or effector T cells. In this model, TCR-MHC interaction strength may dictate differentiation into T_{CM}, T_{EM}, or T_{RM} cells. The second proposed model is the 'One cell, multiple fates' model during which asymmetric cell division occurs allowing the generation of effector and

memory T cells from a single naïve T cell. (Reviewed by Enamorado *et al*).[74]

On cognate antigen recognition, naïve T cells priming in the secondary lymphoid organs (SLOs) leads to their differentiation into T_{RM} precursors. Priming-wise, certain cell types have been described to be involved in T_{RM} cells generation. DC3s, a subset of human DCs $CD1c^+CD163^+CD88^-$ drove the differentiation of $CD103^+CD8^+$ as well as $CD103^+CD4^+$ T cell in vitro via TGF-β production.[75 76] Crosspriming by murine $DNGR\text{-}1^+$ Batf3-dependent DC was reported to be required for committed T_{RM} precursors generation in the LN (lymph node). DNGR-1 mediated cross-presentation provides type 2 (CD24) and 3 (IL-15, IL-12) signals that lead to T-bet induction promoting T_{RM} cells precursors generation and retention in the LN.[77] Additionally, migratory αV-expressing DCs activate and present TGF-β to naïve T cells in the LN, leading to epigenetic preconditioning of these cells to differentiate into epithelial T_{RM}.[78] Monocytes also contribute to T_{RM} cells generation. In an autocrine manner, monocytes produce IL-10 that will be fixed on their cell surface IL-10 receptor.[79 80] Consequently, IL-10 stimulation will lead to TGF-β release resulting in CD103 expression on T cells (figure 3). Recently, novel findings revealed the importance of type 1 Treg in T_{RM} cells development.[81] $CXCR3^+T\text{-}bet^+$ Treg generates bioactive TGF-β necessary for T_{RM} cells differentiation. However, it's important to note that a minor proportion of T_{RM} cells still could be generated in type 1 Treg deficient mice which leads to the hypothesis that other cells may play a role in TGF-β production.[81]

An emerging proof of concept suggests that cytokine milieu might drive T_{RM} cell signature. TGF-β and IL-15 were reported to be key regulators of T_{RM} cells' development and survival (figure 3). IL-15 was essentially reported to assure T_{RM} cell maintenance and persistence.[82] Additionally, IL-15 was shown to promote T_{RM} cells recruitment from SLOs into mucosal sites through the mTOR signaling pathway activation.[83] TGF-β was reported to be a key regulator of T_{RM} cell differentiation and migration (figure 3). TGF-β induces CD103 expression on T_{RM} cells precursors in the gut, SI, lung, and skin.[84–87] During T_{RM} cells development, TGF-β downregulates T-bet expression to a residual level, which is necessary for maintaining IL-15 receptor β-chain (CD122) expression and therefore essential to their long-term persistence.[82] Falling in line with these observations, sequential exposure of T cells to IL-15 and TGF-β induced the development of $CD103^+CD8^+$ T_{RM} cells in the liver.[11] Interestingly, notwithstanding the evident role of TGF-β in the differentiation and retention of T_{RM} cells in peripheral tissues, it has been demonstrated that in SLOs, TGF-β inhibited T_{RM} cells migration and gut homing via α4β7 expression downregulation.[84] Apart from these well-studied cytokines, other inflammatory stimuli such as pro-inflammatory cytokines IL-33, TNF-α, and type I IFN were reported to induce T_{RM} cells differentiation in the peripheral tissues.[74] Interestingly, these stimuli are highly organ-specific, dictated by the inflammatory microenvironment leading to the generation of T_{RM} subsets with different phenotypes and functions. In the GI tract, IL-21 drove the differentiation of highly activated and cytotoxic T_{RM} cells from circulatory precursors only during graft-versus-host disease but not under homeostatic conditions.[88] In murine polyomavirus (MuPyV) brain infection, IL-21 produced by MuPyV high-affinity TCRs $CXCR5^{high}$ $PD\text{-}1^{high}$ $CD4^+$ T cells drove $CD8^+$ T_{RM} cells differentiation in response to viral infection.[17] Additionally, although T_{RM} cells in the skin required TGF-β signaling for their differentiation, the development of T_{RM} cells in the liver was TGF-β independent.[55] Stimuli driving T_{RM} cells' survival and maintenance are also tissue-specific, although IL-2/IL-15 signaling is important for intrahepatic T_{RM} survival, long-term persistence of antigen-specific T_{RM} cells in the epidermal niche is TGF-β dependent.[89]

Taken together, seeing from afar, T_{RM} cells share a core residency program as well as the same differentiation mechanisms regardless of their location, nonetheless, it is now evident that stimuli driving their differentiation and maintenance are dictated by their tissue microenvironment which explains the observed phenotypic, functional, and metabolic heterogeneity as well as persistence across organs.

TRANSCRIPTIONAL REGULATION OF T_{RM} CELLS

Gene expression profiling conducted on T_{RM} cells revealed a unique transcriptional program implicated in the differentiation and maintenance of T_{RM} cells.[19] Six major transcriptional factors have been reported to play a key role in T_{RM} cells transcriptional regulation; Hobit, Blimp1, Runx3, Notch, T-bet, and recently Bhlhe40 (figure 3). Hobit and Blimp1 have been identified as T_{RM}-specific TF that instructs T_{RM} cells differentiation and maintenance in the liver, gut, kidney, and skin by silencing tissue egress genes such as *S1pr1*, *Ccr7*, and *Tcf7*.[27 90–92] Runx3 was also reported to play a role in T_{RM} cells maintenance in a wide range of tissues including the SI. Both in human and mouse, upregulation of Runx3 expression lead to the induction of the core residency signature including expression of tissue retention biomarkers such as CD103 and downregulation of tissue egress ones.[93] Another important TF in T_{RM} regulation is the T-box family member T-bet. Remarkably, T-bet was reported to be down-regulated in T_{RM} cells, which is needed for optimal $CD103^+CD8^+$ T_{RM} maturation. Further, the total shutdown of T-bet leads to decreased survival of T_{RM} cells, which highlights its implication in T_{RM} maintenance. Lung $CD103^+$ T_{RM} cells exhibited an upregulated Notch signaling signature, reported to be required for their differentiation and maintenance.[27 94 95] Interestingly, Blimp1, Runx3, T-bet, and Notch are also key TF implicated in the terminal differentiation of effector T cells and the exhibition of effector functions. This highlights the importance of maintaining an effector function through differentiation into a memory state for T_{RM} cells.

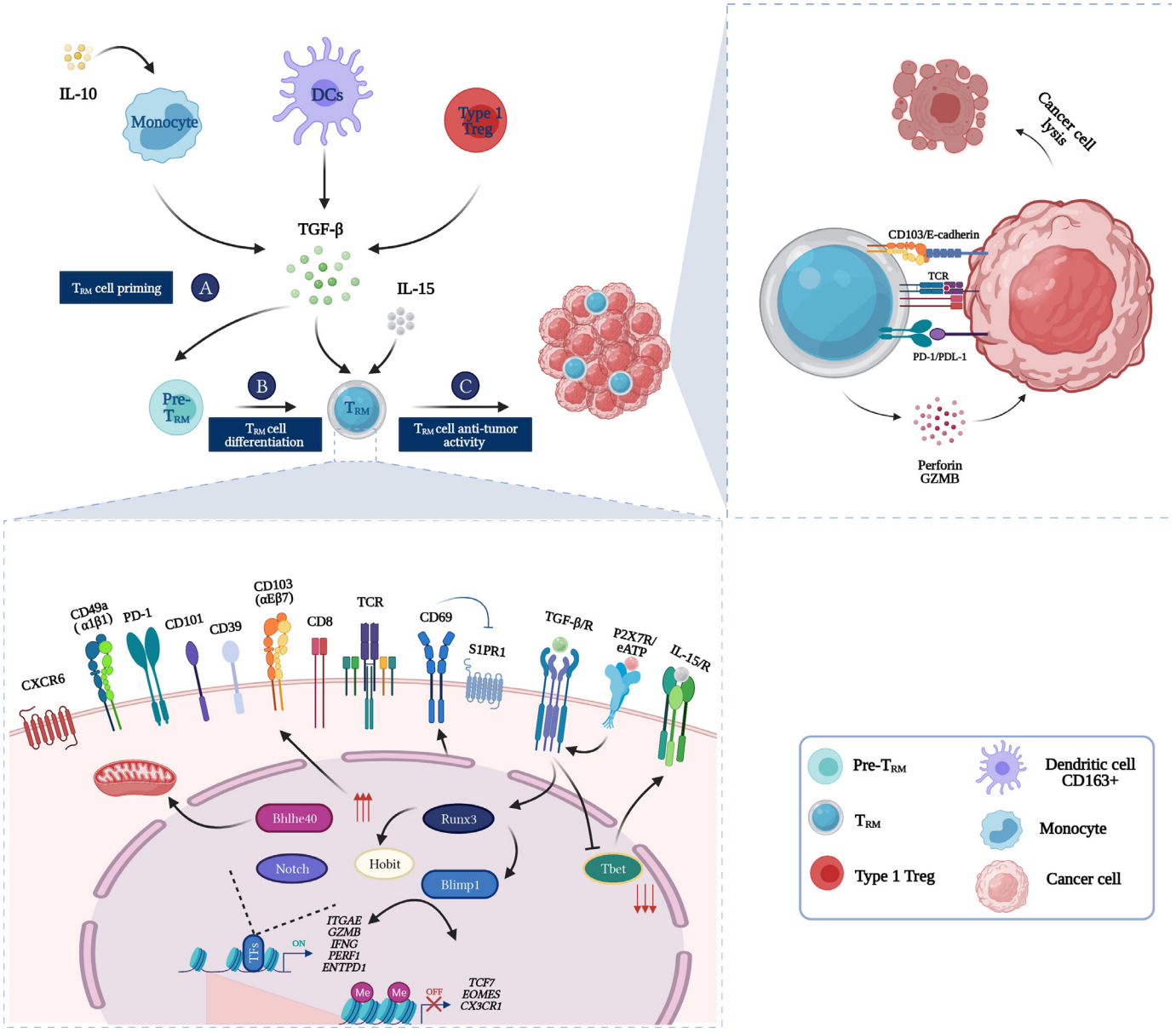

Figure 3 From Zero to Hero: T_{RM} cells in the cancer-immunity cycle. (A) T_{RM} cells precursors are primed in the tumor-draining lymph node by DCs. (B) Once in the tumor microenvironment and in the presence of TGF-β and IL-15, T_{RM} cells precursors will differentiate into T_{RM} cells. Induction of a core residency signature such as expression of tissue retention molecules (CD103, CD69, CD49a, CXCR6) and acquisition of high cytotoxic activity (GZMB, perforin) is under epigenetic regulation and key transcription factors instructions (Blimp1, Hobit, Runx3, Bhlhe40, and Notch). (C) Once fully differentiated, tumor-specific T_{RM} cells can enact cancer cells eradication via an arsenal of cytotoxic molecules such as perforin and granzyme. CD103 expression enables T_{RM} cells biding to E-cadherin expressing tumor cells which sustains the immunological synapse, hence triggering lytic granules polarization and exocytosis. DC, dendritic cell; T_{RM}, tissue-resident memory T cells.

In contrast to T_{CM}, T cell factor 1 (TCF1) is downregulated in T_{RM} cells. Recently, it has been demonstrated that TCF1 binds to the *Itgae* locus and inhibits CD103 expression.[96] Using a global gene expression analysis of *Tcf7* sufficient and *Tcf7* deficient P14 $CD8^+$ T cells, WU *et al* reported an increased expression of CD103 in *Tcf7* deficient cells associated with a decreased expression of tissue egress genes such as *Sell* and *Ccr7*.[96] Finally, Bhlhe40 is another TF that has been recently described.[97] Bhlhe40 or Basic helix-loop-helix family member E40 is a stress-responsive TF that fosters the development, commitment, fitness, and polyfunctionality of T_{RM} cells via metabolic and epigenetic programming.[97] Li *et al* reported that Bhlhe40 drove the expression of several residency genes such as *Cxcr6* and *Itgae* and that loss of Bhlhe40 expression decreased T_{RM} cells in mice as well as TILs survival without impacting circulating T cells function following B16 melanoma challenge.[97 98] Taken together, these observations demonstrate that T_{RM} cells' differentiation and maintenance are controlled by a hybrid transcriptional program of memory and effector cells.

EPIGENETIC REGULATION OF T_{RM} CELLS

Changes in the gene expression profile of T cells are mirrored by a modification in their functional properties. It is well established that epigenetic mechanisms regulate gene expression patterns and dictate whether a gene is expressed or silenced. Of relevance, investigating T_{RM} cells' epigenetic profile will offer a deeper understanding of their phenotype, function, differentiation, and maintenance.

In line with transcriptomic analysis, Assay for Transposase Accessible Chromatin analysis of T_{RM} cells in lung cancer revealed greater chromatin accessibility of CD103 gene promoter (*ITGAE*).[38] Notably, TIM-3$^+$IL-7R$^-$ T_{RM} subset exhibited increased chromatin accessibility of genes encoding the effector molecules IFN-γ as well as granzyme B along with increased accessibility of TIM-3 (*HAVCR2*) and PD-1 (*PDCD1*) loci.[38] Moreover, a study investigating the DNA methylation profile of *PRF1* gene on CD8$^+$ T_{RM} cells in urinary bladder cancer revealed that these cells exhibit signs of exhaustion yet are epigenetically cytotoxic, explained by a low DNA methylation in the reporter CpG site located in the enhancer of the *PRF1* locus.[63]

Genome-wide DNA methylation analysis of tumor-reactive CD8$^+$CD103$^+$CD39$^+$ T cells in CRC has been recently conducted.[69] Interestingly, these cells exhibited hypomethylated regions (HypoMRs) that affected both *ENTPD1* and *ITGAE* along with exhaustion markers encoding genes (*PDCD1*, *LAYN*, and *HAVCR2*). Paired with these observations, TFs binding motifs enrichment analysis of CD103$^+$CD39$^+$ cells revealed 85 significantly enriched TFs binding motifs. Notably, five TFs were particularly overrepresented: BATF, NR4A1, RUNX1, EGR2, and VDR. Unsurprisingly, these TFs are largely associated with T cell exhaustion and CD103 expression. In summary, these epigenetic observations fall in line with previous transcriptomic results, showing hypomethylation of the highly expressed genes encoding for tissue residency, activation, and T cell exhaustion markers, coupled with hypermethylation of tissue egress genes. Altogether, this demonstrates plausible evidence that epigenetic regulation shapes T_{RM} cells molecular features.

T_{RM} ARE STRICTLY NON-RECIRCULATING CELLS: TIME TO THINK TWICE!

T_{RM} cells are a population of immune cells defined as permanent resident cells in non-lymphoid organs without recirculation through SLOs or the blood. However, over the last few years, certain studies have demonstrated that some CD8$^+$ T_{RM} cells in the LN are derived from cells that exit non-lymphoid tissue (NLT),[99] thereby enhancing the accumulation of antigen-specific CD8$^+$ T_{RM} cells in the draining LN. In addition, a recent study conducted on a murine model reported that reactivated T_{RM} cells can indeed rejoin the circulating pool.[100] Strikingly, they reported that T_{RM} cells are not terminally differentiated, and are endowed with certain developmental plasticity that allows them to give rise to T_{CM} and T_{EM} cells. These exciting results give rise to a new 'outside-in' model of protective immune response and reveal an inter-conversion between T_{RM} and T_{CM} cells. In line with these observations, using Hobit lineage tracer mice, Behr *et al* demonstrated that on antigen reencounter, intestinal T_{RM} cells downregulated Hobit giving rise to an ex-Hobit$^+$ circulatory memory subset.[101] These T_{RM} cells-derived offspring referred to as 'ex-T_{RM}' acquired a KLRG1$^+$ CX3CR1$^+$ T_{EM} phenotype that was shown to be transcriptionally and functionally distinct from non-T_{RM}-derived T_{EM} cells. Interestingly, ex-T_{RM} secondary T_{EM} cells presented higher protective potential compared with their non-T_{RM}-derived counterparts. This work gave new insight into the role of T_{RM} cells in shaping not only local but also systemic T cells responses on reinfection. Another intriguing work by Mackay's group showed that T_{RM} cells' plasticity is intertwined with the tissue-specific microenvironment which eventually dictates T_{RM} cells' malleability.[55] In fact, in contrast to CD103$^+$CD69$^+$ skin T_{RM} cells, CD103$^-$CD69$^+$ liver T_{RM} cells were able to trans-differentiate into skin T_{RM} cells on relocation. Additionally, ex-liver T_{RM} cells also showed the capacity to repopulate the circulatory memory pools on restimulation. This is indicative of a restrained trans-differentiation capacity of skin T_{RM} cells and higher plasticity of liver T_{RM} cells. Whereas liver ex-T_{RM} cells showed the capacity to differentiate to both skin and liver T_{RM}, skin ex-T_{RM} cells were less malleable, showing the ability to only differentiate into skin T_{RM} on adoptive transfer. TGF-β was the major driver of this lack of plasticity of skin T_{RM} cells since as discussed above, liver T_{RM} cells do not exhibit TGF-β imprinting. Finally, this T_{RM} cells' developmental plasticity further supports the 'one cell multiple fate' hypothesis previously described. However, these interesting findings need to be validated in the cancer setting, meanwhile, they should be taken with a grain of salt.

T_{RM} CELLS: LOCAL KEY PLAYERS IN GI CANCER IMMUNOSURVEILLANCE

Cancer immunosurveillance is a process whereby the immune system suppresses cancer development and progression.[102] T_{RM} cells' presence has been described in the majority of solid tumors as a sub-population of TILs. Evidence merging from animal models as well as studies of human cancers supported a central role of T_{RM} cells in cancer immunosurveillance. Data from a recent study conducted in a transplantable epicutaneous melanoma mouse model showed that around 40% of mice didn't develop macroscopic lesions for a long period following epicutaneous inoculation.[103] Since the epidermis is hardly accessible by circulating T cells (Tcirc), Park *et al* speculated that T_{RM} cells are responsible for controlling tumor growth independently of Tcirc cells presence. Indeed, they reported the generation of CD8$^+$CD103$^+$CD69$^+$ T_{RM} cells following epicutaneous inoculation in macroscopic lesions-free mice that was correlated with disease

control. Whereas depletion of these T_{RM} cells resulted in tumor growth highlighting the key role of T_{RM} cells in keeping cancer cells dormant and maintaining immune equilibrium.

As previously described, T_{RM} cells are endowed with a cytotoxic activity reported to be higher than non T_{RM} cells. A growing body of evidence supports the hypothesis that T_{RM} cells are able to enact tumor eradication via an arsenal of cytotoxic molecules such as perforin and granzyme (figure 3). In line with these speculations, in lung cancer, ex vivo analysis of T_{RM} cells showed higher co-expression of PD-1 and GZMA and GZMB compared with non-T_{RM} cytotoxic T cells (CTLs).[38] Similarly, the transcriptomic signature of $CD8^+CD103^+CD39^+$ T_{RM} cells in CRC exhibited high expression of genes encoding for cytotoxic proteins such as *GZMA/GZMB* and *PRF1*, probably echoing T_{RM} cells capacity to kill CRC cells and thus controlling tumor growth.[69] In HCC, single-cell analysis revealed that T_{RM} cells represented up to 90% of intrahepatic and intratumoral HBV- specific $CD8^+$ T cells.[73] Interestingly, these subsets were clonally expanded, showed no enrichment in T cell exhaustion signaling pathways, and most importantly their presence was correlated with prolonged relapse-free survival in HCC patients. These results suggest the existence of an anti-tumor immune response imposed by T_{RM} cells. Broadly, these observations evidenced the role of T_{RM} cells in cancer elimination and in maintaining immune equilibrium in certain solid tumors including CRC and HCC.

PROGNOSTIC VALUE OF T_{RM} CELLS IN GI CANCERS

The prognostic value of T_{RM} cells is now well established in several cancer types including melanoma, NSCLC, bladder, ovarian and cervical cancer. The presence of $CD8^+CD103^+$ T_{RM} cells in the TME was associated with a higher overall survival (OS) rate in these cancers.[72]

Unfortunately, the clinical implication of T_{RM} cells in GI cancers remains rudimentary at best. Notwithstanding, a positive correlation between T_{RM} cells infiltration and a favorable prognosis has been reported in certain GI cancers. In a study conducted on a cohort of 165 pancreatic ductal adenocarcinoma patients, IE $CD8^+CD103^+$ over total $CD8^+CD103^+$ cells ratio was significantly associated with improved disease-free survival (DFS) (p=0.022) as well as an improved OS (p=0.009).[42] In CRC, a higher number of $CD8^+CD103^+$ T_{RM} cells was reported to be significantly associated with a better OS rate. In addition, a higher number of $CD8^+CD103^+$ cells was reported to be inversely and significantly associated with distant metastasis.[104] Investigations conducted on HBV-related HCC revealed an enrichment of $CD8^+CD103^+$ T_{RM} cells in the TME, associated with improved OS.[68]

Paired with these results, a recent study conducted on three independent CRC cohorts' datasets revealed that $ITGAE^+CD8^+$ infiltrating lymphocytes were associated with a significantly improved OS (p<0.001). Interestingly, uni and multivariate analysis identified *ITGAE* as an independent prognostic factor for both OS and DFS in CRC patients.[105]

Taken together, these results highlight the key role of T_{RM} cells in mediating improved clinical outcomes of numerous solid cancers including GI ones.

T_{RM} CELLS IN GI CANCER IMMUNOTHERAPY: NEW HOPE OR MORE HYPE

T_{RM} cells: a novel target for checkpoint inhibitors

As outlined above, one common hallmark of T_{RM} cells in healthy tissue as well as in cancer independently of tumor type is the high expression of a wide range of immune checkpoints, such as PD-1, TIM-3, CTLA-4, or LAG-3. This suggests that T_{RM} cells could be a prominent target of immune checkpoint immunotherapy (ICI) therapy and rightfully so. Evaluation of gene expression dataset of nivolumab treated melanoma patients revealed that responders' samples were significantly enriched in T_{RM} signature at baseline.[72] Interestingly, a significant increase of the T_{RM} signature was observed during nivolumab treatment in these patients. Results of the phase 2 NEOSTAR trial conducted on non-small cell lung cancer patients treated with nivolumab or nivolumab plus ipilimumab in the neoadjuvant setting, revealed a considerable increase of $CD103^+CD8^+$ as well as $CD103^+CD4^+$ T_{RM} cells in the patient's group receiving nivolumab plus ipilimumab compared with nivolumab alone.[106] Similar results were observed in the retrospective DISCOVERY cohort involving advanced NSCLC patients treated with anti-PD-1 therapy; accumulation of $CD103^+CD69^+CD8^+$ T_{RM} cells was noticed following anti-PD-1 administration only in responders associated with an improved overall outcome.[107] In line with these observations, analysis of 19 lung cancer biopsies treated with anti-PD-1 therapy showed a significant increase of $CD8^+CD103^+TIM\text{-}3^+IL\text{-}7R^-$ T_{RM} cells in responders compared with non-responders and treatment-naive patients.[38] Paired single-cell transcriptomics with TCR analysis of cytotoxic lymphocytes of responders to anti-PD-1 in post-treatment samples revealed enrichment of *ITGAE* expression as well as *CD38*, *GZMB*, and *GZMH* along with TCR clonal expansion. Parallelly, coupled scRNA-seq-TCR-seq of in vitro expanded mutation-associated neoantigens (MANA) specific TILs revealed that 90% of MANA-specific T cell clones in NSCLC treated with neoadjuvant anti-PD-1 were T_{RM} cells.[108] These MANA-specific T_{RM} were characterized by high expression of CD103, and HOBIT, however, they showed low expression of IL-7R. These results strongly support the hypothesis that anti-PD-1 therapy leads to the expansion of T_{RM} cells endowed with high tumor-neoantigen specificity.

Although the use of ICI is less common in GI cancers compared with melanoma and lung cancers, some emerging studies highlight the predictive value of T_{RM} cells density to ICI. Remarkably, a recent study conducted on esophageal squamous cell carcinoma

(ESCC) revealed that tumor-reactive $CD8^+CD103^+$ T_{RM} cells secreted higher levels of IFN-γ and IL-2 after anti-PD-1 blockade when cultured with tumor cells.[67] Additionally, using an ESCC mouse model, they demonstrated a higher infiltration with $CD8^+CD103^+$ T_{RM} in the TME following anti-PD-1 blockade compared with the control group, which indicates a possible resurrection of T_{RM} cells by the use of checkpoint inhibitors. T_{RM} cells metabolism relies on the oxidation of fatty acids, thus in the TME tumor cells outcompete T_{RM} cells for lipid uptake which induces their apoptosis. In gastric adenocarcinoma the use of anti-PD-L1 in a murine model, not only increased $CD8^+CD103^+$ T_{RM} cells cytotoxicity, it also decreased FABP4 and FABP5 expression on tumor cells, while increasing their expression on T_{RM} cells leading to a metabolic switch and enhanced lipid uptake.[66] This leads us to speculate that along with enhancing T_{RM} cells' anti-tumor effect in gastric adenocarcinoma, PD-L1 blockade reverses the metabolic reprogramming of T_{RM} dictated by tumor cells leading to their improved survival.

All in all, checkpoint inhibitors administration increases T_{RM} cells cytotoxicity and induces their accumulation in several cancer types. There is a growing body of evidence suggesting that $TCF1^+$ $PD\text{-}1^{high}$ TILs represent progenitor subsets that proliferate following ICI. However, TCF1 is downregulated in T_{RM} cells, which leads us to question whether T_{RM} accumulation following anti-PD-1 administration stems from T_{RM} cells reinvigoration or a clonal replacement due to de novo T_{RM} induction remains unclear and needs to be investigated.

Noteworthy, T_{RM} cells' presence could represent a double-edged sword when it comes to ICI use. Recent studies revealed that T_{RM} cells play a key role in ICI-induced colitis (ICI-colitis), one of the most common immune-related adverse events. Investigating normal and inflamed colon of anti-PD-1/CTLA-4 treated melanoma patients, Luoma *et al* reported a striking accumulation of highly cytotoxic $CD8^+$ T cells in ICI-colitis.[109] Interestingly, the use of coupled scRNA-seq-TCR-seq revealed that ICI-colitis is associated with a shift of T_{RM} cells to effector T cells with high immune checkpoints expression and high cytotoxicity. In addition, a recent study revealed that activated $CD8^+$ T_{RM} cells represented the key effector cells in ICI-colitis.[110] The presence of T_{RM} cells was correlated with endoscopic and clinical ICI-colitis severity. These T_{RM} cells were characterized by high production of IFN-γ associated with high expression of immune checkpoints such as PD-1, CTLA-4, LAG-3, and TIM-3.

In summary, ICI use is emerging as a promising therapeutic strategy for 'hot' GI cancers mainly characterized by having a MSI and anti-PD-1 treatments are currently FDA approved in the metastatic setting.[111] We previously discussed that T_{RM} cells represent an important subset of TILs in CRC, HCC, and pancreatic cancer. Therefore, T_{RM} cells can represent an interesting population to target in these cancers and the presence of T_{RM} cells might be used in a predictive setting in order to stratify responders and non-responders to this therapeutic strategy (figure 4).

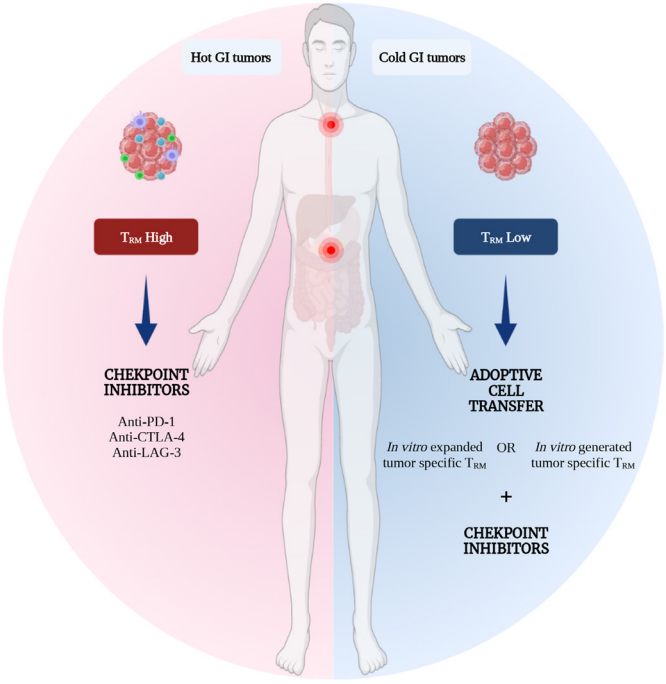

Figure 4 T_{RM} cells as a tool for GI cancers immunotherapy. T_{RM} cells are emerging as long persisting potent cytotoxic T cells destined for tissue residency, making them a hot target for cancer immunotherapy in general and GI cancers in particular. This is a representation of the potential therapeutic strategies where T_{RM} cells could be incorporated into GI cancers standard treatment paradigms. For immune infiltrated or the so-called 'hot' GI tumors, T_{RM} cells could serve as a predictive factor as well as a target for checkpoint inhibitors. For the therapeutically challenging 'cold' GI tumors, in vitro expanded or generated $CXCR6^+$ tumor-specific T_{RM} cells could be adoptively transferred in combination or not with checkpoint inhibitors. GI, gastrointestinal; T_{RM}, tissue-resident memory T cells.

T_{RM} in adoptive cells transfer

GI cancers are considered cold tumors with limited access to checkpoint inhibitors.[112] Therefore, adoptive cell transfer (ACT) is being considered as one of the most promising therapeutic strategies for patients with cold cancers. One of the major challenges for ACT is the ability of T cells to infiltrate the tumor and to be able to persist long-term, both of which constitute the hallmark features of T_{RM} cells. Additionally, due to their observed in vitro functionality and cytotoxicity, T_{RM} cells are gaining the researcher's attention as a potent candidate for ACT. A recent study showed that in vitro generated NY-ESO1/SSX2 specific $CD8^+CD103^+$ presented a faster cancer recognition as well as cytotoxicity compared with $CD8^+CD103^-$ non T_{RM} cells.[113] Interestingly, they were also endowed with high energetic potential. These data gave new evidence for T_{RM} cells' antitumor efficacy compared with non T_{RM} cells which makes them a promising candidate for ACT, especially in GI cancers (figure 4). Although

ACT of in vitro expanded TILs showed promising results, only a minor fraction of treated patients achieved durable responses. As previously discussed, TILs represent an heterogenous T cells populations encountering tumor-specific as well as bystander T cells which may explain the limited success of the use of the unfractionated TILs populations for ACT.[114] Recent studies revealed that whether in HBV-induced liver cancer or NSCLC, T_{RM} cells represented the tumor antigen-specific population of TILs, therefore tetramer sorting and in vitro expansion of these cells with potent anti-tumor properties may represent a better therapeutic strategy for solid cancers.[114 115] One of the major challenges impeding the use of CAR-T cells in solid tumors is their restrained trafficking and persistence in the TME. T_{RM} on the other hand represent highly cytotoxic, long-lived T cells endowed with the expression of tissue homing biomarkers and the down-regulation of tissue egress ones, which represent highly desired properties when designing T cell-based therapies for solid tumors, GI included. Additionally, to overcome tissue homing challenges, beyond intravenous transfusion, intratumoral injection of T_{RM} cells could be considered. Last but not least, since our understanding of T_{RM} cells generation has evolved substantially over the last years, in vitro generation of tumor antigen-specific T_{RM} cells from the patient's peripheral blood could represent an easily accessible therapeutic strategy. Furthermore, since T_{RM} cells phenotype is tissue-specific, the generation of T_{RM} cells with organ-specific homing biomarkers ($CXCR6^+$ T_{RM} for liver cancer/metastasis, $CD103^+$ T_{RM} for CRC…) would represent an intriguing approach for improving clinical responses. T_{RM} cells have emerged as the predominant tumor antigen-specific TILs population, they are endowed with high cytotoxicity, tissue-homing ability, and long-term persistence. The success of ACT is built on these duly warranted hallmarks, clinical studies using tumor antigen-specific T_{RM} cells are critically needed especially for cold tumors such as GI cancers.

CONCLUSIONS AND FUTURE PERSPECTIVES

T_{RM} research has been gaining huge momentum lately. It's now well established that T_{RM} cells patrol the TME, and they can promote both cancer elimination and equilibrium. Remarkably, immune infiltrated GI tumors were enriched in T_{RM} cells which represented a better indicator of the patient's prognosis. Moreover, they were predictive of checkpoint inhibitors' response. However, the importance of leveraging this proof of concept into cancer treatment will require further understanding of T_{RM} function, the molecular network that drives their development and maintenance in the TME, the transcriptional regulation behind their exhaustion status, and first and foremost identification of solid biomarkers that enable to distinguish between T_{RM} cells from conventional TILs subsets. Of note, single-cell analysis helped to gain a more comprehensive understanding of T_{RM} cells heterogeneity, therefore, the use of this technology should be widespread to a larger panel of GI cancers. Once we got exhaustive answers to these questions, capitalizing on T_{RM} cells will be an exciting therapeutic approach to turning 'cold' GI tumors 'hot'.

Contributors Conceptualization: CB and SAb. Writing: SAb and SAr. Review and editing: CB, SAb, MK, RL, MBK, AV, AD, and BH.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Jin M-Z, Jin W-L. The updated landscape of tumor microenvironment and drug repurposing. *Sig Transduct Target Ther* 2020;5:1–16.
2 Duan Q, Zhang H, Zheng J, *et al*. Turning cold into hot: firing up the tumor microenvironment. *Trends Cancer* 2020;6:605–18.
3 Galon J, Costes A, Sanchez-Cabo F, *et al*. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;313:1960–4.
4 Galon J, Fridman W-H, Pagès F. The adaptive immunologic microenvironment in colorectal cancer: a novel perspective. *Cancer Res* 2007;67:1883–6.
5 Mlecnik B, Bindea G, Angell HK, *et al*. Integrative analyses of colorectal cancer show immunoscore is a stronger predictor of patient survival than microsatellite instability. *Immunity* 2016;44:698–711.
6 Sallusto F, Lenig D, Förster R, *et al*. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. *Nature* 1999;401:708–12.
7 Gebhardt T, Wakim LM, Eidsmo L, *et al*. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat Immunol* 2009;10:524–30.
8 Masopust D, Choo D, Vezys V, *et al*. Dynamic T cell migration program provides resident memory within intestinal epithelium. *J Exp Med* 2010;207:553–64.
9 Urban SL, Jensen IJ, Shan Q, *et al*. Peripherally induced brain tissue-resident memory $CD8^+$ T cells mediate protection against CNS infection. *Nat Immunol* 2020;21:938–49.
10 Steinbach K, Vincenti I, Kreutzfeldt M, *et al*. Brain-resident memory T cells represent an autonomous cytotoxic barrier to viral infection. *J Exp Med* 2016;213:1571–87.
11 Pallett LJ, Davies J, Colbeck EJ, *et al*. IL-2^{high} tissue-resident T cells in the human liver: Sentinels for hepatotropic infection. *J Exp Med* 2017;214:1567–80.
12 Zaid A, Mackay LK, Rahimpour A, *et al*. Persistence of skin-resident memory T cells within an epidermal niche. *Proc Natl Acad Sci U S A* 2014;111:5307–12.
13 Masopust D, Jiang J, Shen H, *et al*. Direct analysis of the dynamics of the intestinal mucosa CD8 T cell response to systemic virus infection. *J Immunol* 2001;166:2348–56.
14 Hogan RJ, Usherwood EJ, Zhong W, *et al*. Activated antigen-specific CD8+ T cells persist in the lungs following recovery from respiratory virus infections. *J Immunol* 2001;166:1813–22.
15 Kiniry BE, Li S, Ganesh A, *et al*. Detection of HIV-1-specific gastrointestinal tissue resident $CD8^+$ T-cells in chronic infection. *Mucosal Immunol* 2018;11:909–20.
16 Weisberg SP, Carpenter DJ, Chait M, *et al*. Tissue-Resident memory T cells mediate immune homeostasis in the human pancreas through the PD-1/PD-L1 pathway. *Cell Rep* 2019;29:3916–32.
17 Ren HM, Kolawole EM, Ren M, *et al*. Il-21 from high-affinity CD4 T cells drives differentiation of brain-resident CD8 T cells during persistent viral infection. *Sci Immunol* 2020;5:eabb5590.
18 Bottois H, Ngollo M, Hammoudi N, *et al*. Klrg1 and CD103 expressions define distinct intestinal tissue-resident memory

CD8 T cell subsets modulated in Crohn's disease. *Front Immunol* 2020;11:896.
19 Mackay LK, Rahimpour A, Ma JZ, *et al*. The developmental pathway for CD103(+)CD8+ tissue-resident memory T cells of skin. *Nat Immunol* 2013;14:1294–301.
20 Liao W, Liu Y, Ma C, *et al*. The downregulation of IL-18R defines bona fide kidney-resident CD8$^+$ T cells. *iScience* 2021;24:101975.
21 Smolders J, Heutinck KM, Fransen NL, *et al*. Tissue-Resident memory T cells populate the human brain. *Nat Commun* 2018;9:4593.
22 Piet B, de Bree GJ, Smids-Dierdorp BS, *et al*. Cd8$^+$ T cells with an intraepithelial phenotype upregulate cytotoxic function upon influenza infection in human lung. *J Clin Invest* 2011;121:2254–63.
23 Kumar BV, Ma W, Miron M, *et al*. Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. *Cell Rep* 2017;20:2921–34.
24 Han S-J, Glatman Zaretsky A, Andrade-Oliveira V, *et al*. White adipose tissue is a reservoir for memory T cells and promotes protective memory responses to infection. *Immunity* 2017;47:1154–68.
25 Thom JT, Weber TC, Walton SM, *et al*. The Salivary Gland Acts as a Sink for Tissue-Resident Memory CD8(+) T Cells, Facilitating Protection from Local Cytomegalovirus Infection. *Cell Rep* 2015;13:1125–36.
26 Stolp B, Thelen F, Ficht X, *et al*. Salivary gland macrophages and tissue-resident CD8$^+$ T cells cooperate for homeostatic organ surveillance. *Sci Immunol* 2020;5:eaaz4371.
27 Behr FM, Chuwonpad A, Stark R, *et al*. Armed and ready: transcriptional regulation of tissue-resident memory CD8 T cells. *Front Immunol* 2018;9:9.
28 Cepek KL, Shaw SK, Parker CM, *et al*. Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alpha E beta 7 integrin. *Nature* 1994;372:190–3.
29 Wagner N, Löhler J, Kunkel EJ, *et al*. Critical role for beta7 integrins in formation of the gut-associated lymphoid tissue. *Nature* 1996;382:366–70.
30 Shiow LR, Rosen DB, Brdicková N, *et al*. Cd69 acts downstream of interferon-alpha/beta to inhibit S1P1 and lymphocyte egress from lymphoid organs. *Nature* 2006;440:540–4.
31 Cibrián D, Sánchez-Madrid F. Cd69: from activation marker to metabolic gatekeeper. *Eur J Immunol* 2017;47:946–53.
32 Szabo PA, Levitin HM, Miron M, *et al*. Single-Cell transcriptomics of human T cells reveals tissue and activation signatures in health and disease. *Nat Commun* 2019;10:4706.
33 Wein AN, McMaster SR, Takamura S, *et al*. Cxcr6 regulates localization of tissue-resident memory CD8 T cells to the airways. *J Exp Med* 2019;216:2748–62.
34 Roberts AI, Brolin RE, Ebert EC. Integrin alpha1beta1 (VLA-1) mediates adhesion of activated intraepithelial lymphocytes to collagen. *Immunology* 1999;97:679–85.
35 Reilly EC, Lambert Emo K, Buckley PM, *et al*. T_{RM} integrins CD103 and CD49a differentially support adherence and motility after resolution of influenza virus infection. *Proc Natl Acad Sci U S A* 2020;117:12306–14.
36 Bromley SK, Akbaba H, Mani V, *et al*. CD49a Regulates Cutaneous Resident Memory CD8$^+$ T Cell Persistence and Response. *Cell Rep* 2020;32:108085.
37 Cheuk S, Schlums H, Gallais Sérézal I, *et al*. CD49a Expression Defines Tissue-Resident CD8$^+$ T Cells Poised for Cytotoxic Function in Human Skin. *Immunity* 2017;46:287–300.
38 Clarke J, Panwar B, Madrigal A, *et al*. Single-Cell transcriptomic analysis of tissue-resident memory T cells in human lung cancer. *J Exp Med* 2019;216:2128–49.
39 Zuber J, Shonts B, Lau S-P, *et al*. Bidirectional intragraft alloreactivity drives the repopulation of human intestinal allografts and correlates with clinical outcome. *Sci Immunol* 2016;1:eaah3732.
40 Bartolomé-Casado R, Landsverk OJB, Chauhan SK, *et al*. Resident memory CD8 T cells persist for years in human small intestine. *J Exp Med* 2019;216:2412–26.
41 Clark RA, Watanabe R, Teague JE, *et al*. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. *Sci Transl Med* 2012;4:117ra7.
42 Lohneis P, Sinn M, Bischoff S, *et al*. Cytotoxic tumour-infiltrating T lymphocytes influence outcome in resected pancreatic ductal adenocarcinoma. *Eur J Cancer* 2017;83:290–301.
43 Ling K-L, Dulphy N, Bahl P, *et al*. Modulation of CD103 expression on human colon carcinoma-specific CTL. *J Immunol* 2007;178:2908–15.
44 Quinn E, Hawkins N, Yip YL, *et al*. CD103+ intraepithelial lymphocytes--a unique population in microsatellite unstable sporadic colorectal cancer. *Eur J Cancer* 2003;39:469–75.
45 Ghilas S, Valencia-Hernandez A-M, Enders MH, *et al*. Resident memory T cells and their role within the liver. *Int J Mol Sci* 2020;21:E8565.
46 Schenkel JM, Fraser KA, Beura LK, *et al*. T cell memory. resident memory CD8 T cells trigger protective innate and adaptive immune responses. *Science* 2014;346:98–101.
47 Sheridan BS, Pham Q-M, Lee Y-T, *et al*. Oral infection drives a distinct population of intestinal resident memory CD8(+) T cells with enhanced protective function. *Immunity* 2014;40:747–57.
48 Behr FM, Beumer-Chuwonpad A, Kragten NAM, *et al*. Circulating memory CD8$^+$ T cells are limited in forming CD103$^+$ tissue-resident memory T cells at mucosal sites after reinfection. *Eur J Immunol* 2021;51:151–66.
49 Konjar Špela, Frising UC, Ferreira C, *et al*. Mitochondria maintain controlled activation state of epithelial-resident T lymphocytes. *Sci Immunol* 2018;3:eaan2543.
50 Milner JJ, Toma C, He Z, *et al*. Heterogenous Populations of Tissue-Resident CD8$^+$ T Cells Are Generated in Response to Infection and Malignancy. *Immunity* 2020;52:808–24.
51 FitzPatrick MEB, Provine NM, Garner LC, *et al*. Human intestinal tissue-resident memory T cells comprise transcriptionally and functionally distinct subsets. *Cell Rep* 2021;34:108661.
52 Robinson MW, Harmon C, O'Farrelly C. Liver immunology and its role in inflammation and homeostasis. *Cell Mol Immunol* 2016;13:267–76.
53 McNamara HA, Cai Y, Wagle MV, *et al*. Up-Regulation of LFA-1 allows liver-resident memory T cells to patrol and remain in the hepatic sinusoids. *Sci Immunol* 2017;2:eaaj1996.
54 Stelma F, de Niet A, Sinnige MJ, *et al*. Human intrahepatic CD69+CD8+ T cells have a tissue resident memory T cell phenotype with reduced cytolytic capacity. *Sci Rep* 2017;7:6172.
55 Christo SN, Evrard M, Park SL, *et al*. Discrete tissue microenvironments instruct diversity in resident memory T cell function and plasticity. *Nat Immunol* 2021;22:1140–51.
56 Wiggins BG, Pallett LJ, Li X, *et al*. The human liver microenvironment shapes the homing and function of CD4$^+$ T-cell populations. *Gut* 2021. doi:10.1136/gutjnl-2020-323771. [Epub ahead of print: 21 Sep 2021].
57 Bartolomé-Casado R, Landsverk OJB, Chauhan SK, *et al*. CD4$^+$ T cells persist for years in the human small intestine and display a T_H1 cytokine profile. *Mucosal Immunol* 2021;14:402–10.
58 Frizzell H, Fonseca R, Christo SN, *et al*. Organ-Specific isoform selection of fatty acid-binding proteins in tissue-resident lymphocytes. *Sci Immunol* 2020;5:eaay9283.
59 Edwards J, Wilmott JS, Madore J, *et al*. CD103 $^+$ Tumor-Resident CD8 $^+$ T Cells Are Associated with Improved Survival in Immunotherapy-Naïve Melanoma Patients and Expand Significantly During Anti–PD-1 Treatment. *Clinical Cancer Research* 2018;24:3036–45.
60 Ganesan A-P, Clarke J, Wood O, *et al*. Tissue-Resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. *Nat Immunol* 2017;18:940–50.
61 Duhen T, Duhen R, Montler R, *et al*. Co-Expression of CD39 and CD103 identifies tumor-reactive CD8 T cells in human solid tumors. *Nat Commun* 2018;9:2724.
62 Wang B, Wu S, Zeng H, *et al*. CD103+ tumor infiltrating lymphocytes predict a favorable prognosis in urothelial cell carcinoma of the bladder. *J Urol* 2015;194:556–62.
63 Hartana CA, Ahlén Bergman E, Broomé A, *et al*. Tissue-Resident memory T cells are epigenetically cytotoxic with signs of exhaustion in human urinary bladder cancer. *Clin Exp Immunol* 2018;194:39–53.
64 Anz D, Mueller W, Golic M, *et al*. CD103 is a hallmark of tumor-infiltrating regulatory T cells. *Int J Cancer* 2011;129:2417–26.
65 Shekhar S, Yang X. Pulmonary CD103+ dendritic cells: key regulators of immunity against infection. *Cell Mol Immunol* 2020;17:670–1.
66 Lin R, Zhang H, Yuan Y, *et al*. Fatty Acid Oxidation Controls CD8$^+$ Tissue-Resident Memory T-cell Survival in Gastric Adenocarcinoma. *Cancer Immunol Res* 2020;8:479–92.
67 Han L, Gao Q-L, Zhou X-M, *et al*. Characterization of CD103$^+$ CD8$^+$ tissue-resident T cells in esophageal squamous cell carcinoma: may be tumor reactive and resurrected by anti-PD-1 blockade. *Cancer Immunol Immunother* 2020;69:1493–504.
68 Lim CJ, Lee YH, Pan L, *et al*. Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. *Gut* 2019;68:916–27.

69 Yang R, Cheng S, Luo N, *et al*. Distinct epigenetic features of tumor-reactive CD8+ T cells in colorectal cancer patients revealed by genome-wide DNA methylation analysis. *Genome Biol* 2019;21:2.
70 Blank CU, Haining WN, Held W, *et al*. Defining 'T cell exhaustion'. *Nat Rev Immunol* 2019;19:665–74.
71 Franco F, Jaccard A, Romero P, *et al*. Metabolic and epigenetic regulation of T-cell exhaustion. *Nat Metab* 2020;2:1001–12.
72 Savas P, Virassamy B, Ye C, *et al*. Single-Cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. *Nat Med* 2018;24:986–93.
73 Cheng Y, Gunasegaran B, Singh HD, *et al*. Non-terminally exhausted tumor-resident memory HBV-specific T cell responses correlate with relapse-free survival in hepatocellular carcinoma. *Immunity* 2021;54:1825–40.
74 Enamorado M, Khouili SC, Iborra S, *et al*. Genealogy, Dendritic Cell Priming, and Differentiation of Tissue-Resident Memory CD8$^+$ T Cells. *Front Immunol* 2018;9:9.
75 Bourdely P, Anselmi G, Vaivode K, *et al*. Transcriptional and functional analysis of CD1c+ human dendritic cells identifies a CD163+ subset priming CD8+CD103+ T cells. *Immunity* 2020;53:335–52.
76 Yu CI, Becker C, Wang Y, *et al*. Human CD1c+ dendritic cells drive the differentiation of CD103+ CD8+ mucosal effector T cells via the cytokine TGF-β. *Immunity* 2013;38:818–30.
77 Iborra S, Martínez-López M, Khouili SC, *et al*. Optimal Generation of Tissue-Resident but Not Circulating Memory T Cells during Viral Infection Requires Crosspriming by DNGR-1$^+$ Dendritic Cells. *Immunity* 2016;45:847–60.
78 Mani V, Bromley SK, Äijö T, *et al*. Migratory DCs activate TGF-β to precondition naïve CD8$^+$ T cells for tissue-resident memory fate. *Science* 2019;366:eaav5728.
79 Thompson EA, Darrah PA, Foulds KE, *et al*. Monocytes acquire the ability to prime tissue-resident T cells via IL-10-Mediated TGF-β release. *Cell Rep* 2019;28:1127–35.
80 Chu K-L, Batista NV, Girard M, *et al*. Monocyte-Derived cells in tissue-resident memory T cell formation. *J Immunol* 2020;204:477–85.
81 Ferreira C, Barros L, Baptista M, *et al*. Type 1 T_{reg} cells promote the generation of CD8$^+$ tissue-resident memory T cells. *Nat Immunol* 2020;21:766–76.
82 Mackay LK, Wynne-Jones E, Freestone D, *et al*. T-Box transcription factors combine with the cytokines TGF-β and IL-15 to control tissue-resident memory T cell fate. *Immunity* 2015;43:1101–11.
83 Sowell RT, Goldufsky JW, Rogozinska M, *et al*. Il-15 complexes induce migration of resting memory CD8 T cells into mucosal tissues. *J Immunol* 2017;199:2536–46.
84 Zhang N, Bevan MJ. Transforming growth factor-β signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. *Immunity* 2013;39:687–96.
85 Lee Y-T, Suarez-Ramirez JE, Wu T, *et al*. Environmental and antigen receptor-derived signals support sustained surveillance of the lungs by pathogen-specific cytotoxic T lymphocytes. *J Virol* 2011;85:4085–94.
86 El-Asady R, Yuan R, Liu K, *et al*. TGF-{beta}-dependent CD103 expression by CD8(+) T cells promotes selective destruction of the host intestinal epithelium during graft-versus-host disease. *J Exp Med* 2005;201:1647–57.
87 Qiu Z, Chu TH, Sheridan BS. TGF-β: Many Paths to CD103$^+$ CD8 T Cell Residency. *Cells* 2021;10:989.
88 Tkachev V, Kaminski J, Potter EL, *et al*. Spatiotemporal single-cell profiling reveals that invasive and tissue-resident memory donor CD8$^+$ T cells drive gastrointestinal acute graft-versus-host disease. *Sci Transl Med* 2021;13:eabc0227.
89 Hirai T, Yang Y, Zenke Y, *et al*. Competition for active TGFβ cytokine allows for selective retention of antigen-specific tissue- resident memory T cells in the epidermal niche. *Immunity* 2021;54:84–98.
90 Mackay LK, Minnich M, Kragten NAM, *et al*. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science* 2016;352:459–63.
91 Behr FM, Kragten NAM, Wesselink TH, *et al*. Blimp-1 Rather Than Hobit Drives the Formation of Tissue-Resident Memory CD8$^+$ T Cells in the Lungs. *Front Immunol* 2019;10:400.
92 Zundler S, Becker E, Spocinska M, *et al*. Hobit- and Blimp-1-driven CD4$^+$ tissue-resident memory T cells control chronic intestinal inflammation. *Nat Immunol* 2019;20:288–300.
93 Milner JJ, Toma C, Yu B, *et al*. Runx3 programs CD8$^+$ T cell residency in non-lymphoid tissues and tumours. *Nature* 2017;552:253–7.
94 Hombrink P, Helbig C, Backer RA, *et al*. Programs for the persistence, vigilance and control of human CD8$^+$ lung-resident memory T cells. *Nat Immunol* 2016;17:1467–78.
95 Szabo PA, Miron M, Farber DL. Location, location, location: tissue resident memory T cells in mice and humans. *Sci Immunol* 2019;4:eaas9673.
96 Wu J, Madi A, Mieg A, *et al*. T cell factor 1 suppresses CD103+ lung tissue-resident memory T cell development. *Cell Rep* 2020;31:107484.
97 Li C, Zhu B, Son YM, *et al*. The Transcription Factor Bhlhe40 Programs Mitochondrial Regulation of Resident CD8$^+$ T Cell Fitness and Functionality. *Immunity* 2019;51:491–507.
98 Park SL, Mackay LK. Bhlhe40 keeps resident T cells too fit to quit. *Immunity* 2019;51:418–20.
99 Beura LK, Wijeyesinghe S, Thompson EA, *et al*. T cells in nonlymphoid tissues give rise to Lymph-Node-Resident memory T cells. *Immunity* 2018;48:327–38.
100 Fonseca R, Beura LK, Quarnstrom CF, *et al*. Developmental plasticity allows outside-in immune responses by resident memory T cells. *Nat Immunol* 2020;21:412–21.
101 Behr FM, Parga-Vidal L, Kragten NAM, *et al*. Tissue-resident memory CD8$^+$ T cells shape local and systemic secondary T cell responses. *Nat Immunol* 2020;21:1070–81.
102 O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat Rev Clin Oncol* 2019;16:151–67.
103 Park SL, Buzzai A, Rautela J, *et al*. Tissue-resident memory CD8$^+$ T cells promote melanoma-immune equilibrium in skin. *Nature* 2019;565:366–71.
104 Hu W, Sun R, Chen L, *et al*. Prognostic significance of resident CD103$^+$CD8$^+$T cells in human colorectal cancer tissues. *Acta Histochem* 2019;121:657–63.
105 Hu X, Li Y-Q, Li Q-G, *et al*. ITGAE defines CD8+ tumor-infiltrating lymphocytes predicting a better prognostic survival in colorectal cancer. *EBioMedicine* 2018;35:178–88.
106 Cascone T, William WN, Weissferdt A, *et al*. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. *Nat Med* 2021;27:504–14.
107 Corgnac S, Malenica I, Mezquita L, *et al*. CD103$^+$CD8$^+$$T_{RM}$ Cells Accumulate in Tumors of Anti-PD-1-Responder Lung Cancer Patients and Are Tumor-Reactive Lymphocytes Enriched with Tc17. *Cell Rep Med* 2020;1:100127.
108 Caushi JX, Zhang J, Ji Z, *et al*. Transcriptional programs of neoantigen-specific TIL in anti-PD-1-treated lung cancers. *Nature* 2021;596:126–32.
109 Luoma AM, Suo S, Williams HL, *et al*. Molecular pathways of colon inflammation induced by cancer immunotherapy. *Cell* 2020;182:655–71.
110 Sasson SC, Slevin SM, Cheung VTF, *et al*. Interferon-Gamma-Producing CD8$^+$ Tissue Resident Memory T Cells Are a Targetable Hallmark of Immune Checkpoint Inhibitor-Colitis. *Gastroenterology* 2021;161:1229–44.
111 Riedl JM, Stotz M, Gerger A. Role of immune checkpoint inhibitors in gastrointestinal cancer treatment. *Memo* 2019;12:71–6.
112 Lu Z, Peng Z, Liu C, *et al*. Current status and future perspective of immunotherapy in gastrointestinal cancers. *Innovation* 2020;1:100041.
113 Abd Hamid M, Colin-York H, Khalid-Alham N, *et al*. Self-Maintaining CD103$^+$ Cancer-Specific T Cells Are Highly Energetic with Rapid Cytotoxic and Effector Responses. *Cancer Immunol Res* 2020;8:203–16.
114 Beumer-Chuwonpad A, Taggenbrock RLRE, Ngo TA, *et al*. The potential of tissue-resident memory T cells for adoptive immunotherapy against cancer. *Cells* 2021;10:2234.
115 Okła K, Farber DL, Zou W. Tissue-Resident memory T cells in tumor immunity and immunotherapy. *J Exp Med* 2021;218:e20201605.