REVIEW ARTICLE

# Local heroes or villains: tissue-resident memory T cells in human health and disease

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Tissue-resident memory T ($T_{RM}$) cells are increasingly associated with the outcomes of health and disease. $T_{RM}$ cells can mediate local immune protection against infections and cancer, which has led to interest in $T_{RM}$ cells as targets for vaccination and immunotherapies. However, these cells have also been implicated in mediating detrimental pro-inflammatory responses in autoimmune skin diseases such as psoriasis, alopecia areata, and vitiligo. Here, we summarize the biology of $T_{RM}$ cells established in animal models and in translational human studies. We review the beneficial effects of $T_{RM}$ cells in mediating protective responses against infection and cancer and the adverse role of $T_{RM}$ cells in driving pathology in autoimmunity. A further understanding of the breadth and mechanisms of $T_{RM}$ cell activity is essential for the safe design of strategies that manipulate $T_{RM}$ cells, such that protective responses can be enhanced without unwanted tissue damage, and pathogenic $T_{RM}$ cells can be eliminated without losing local immunity.

**Keywords:** human; T cells; tissue-resident; memory; immunity

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## INTRODUCTION

Improving the quality and breadth of immunity has been an ongoing challenge for the long-term preservation of human health. Much of the focus has been directed at generating immunological memory, a paradigm demonstrated to be effective at protecting against recurrent pathological challenges in an ever-evolving environment. A critical component of this process is a population of non-recirculating lymphocytes, termed tissue-resident memory T ($T_{RM}$) cells, which are phenotypically and transcriptionally distinct from circulating memory T cells[1] and offer front-line protection against invading microbes and tumor outgrowth.[2,3] While the majority of studies detailing the identity and differentiation of $T_{RM}$ cells have been performed in mouse models,[4–8] more recent studies of human tissues describe the association of $T_{RM}$ cell density and phenotype with prognosis in several disease settings.[9–11] Human $T_{RM}$ cells have heterogeneous developmental and survival requirements, the full extent of which is yet to be completely elucidated, demonstrating a continued need to further dissect fundamental mechanisms of $T_{RM}$ cell biology. Here, we discuss what is known about human $T_{RM}$ cells in health and in disease in the context of infection, cancer, autoimmunity, and transplantation, highlighting knowledge gaps and therapeutic opportunities.

## AN OVERVIEW OF $T_{RM}$ CELLS: LESSONS FROM MICE

$T_{RM}$ cells have been investigated across multiple tissues and in various disease settings. Studies from murine models using transplantation,[5,12] parabiosis,[13–15] and intravascular labeling[15,16] have demonstrated a *bona fide* resident population of memory T cells that are permanently lodged in the tissue. While the majority of studies have focused on $CD8^+$ $T_{RM}$ cells, there is increasing evidence that $CD4^+$ $T_{RM}$ cells are also present in nonlymphoid tissues in both mice[17–21] and humans.[22–25] The defining feature of $T_{RM}$ cells is their commitment to the tissue of residence (as opposed to any particular marker), a key feature being their inability to circulate through the bloodstream or lymphatics. $T_{RM}$ cells lack the lymph node homing molecules CD62L and CCR7,[6,26] which helps to facilitate tissue residency and downregulate the transcription factor KLF2[27] and receptors of sphingosine-1-phosphate (S1P), a chemoattractant produced by endothelial cells that promotes egress from lymph nodes and tissue.[28] Moreover, the expression of CD69, which is commonly used to define $T_{RM}$ cells, has a role in antagonizing the expression of the egress receptor S1P receptor 1 (S1PR1) and preventing cells from migrating out of the tissue.[27,29]

The canonical markers associated with $CD8^+$ $T_{RM}$ cells are CD69 and integrin CD103, although $T_{RM}$ cell populations lacking CD103 have also been detected in tissues, including the kidney[30] and liver[31,32] and the small intestine intraepithelial lymphocytes (SI-IELs) and lamina propria.[33,34] The expression of other surface molecules has been associated with $CD8^+$ $T_{RM}$ cells, including CD49a, CD101, PD-1, and CXCR6,[10,35–37] some of which are dependent on the local tissue. Following entry into nonlymphoid organs, $T_{RM}$ cells acquire several differentiation markers in a process that involves the action of cytokines, including tumor growth factor-β (TGFβ) and interleukin-15 (IL-15). Using T cells from mice deficient in cytokines or their receptors, it has been demonstrated that TGFβ plays a role

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in the development of $T_{RM}$ cells in the skin,[6,7] lung,[7,38] salivary gland,[39,40] and SI-IELs[34,41] and that IL-15 contributes to $T_{RM}$ cell development in the skin, salivary gland, lung, and liver (but not in SI-IELs[8]). Importantly, it has been shown that other tissue-resident cells (including natural killer and natural killer T cells) share a common transcriptional signature regulated by the transcription factors Hobit and Blimp-1, which are distinct from the genetic profile of circulating memory T cells.[31] Both the Notch family of signaling receptors and the aryl hydrocarbon receptor play a role in the maintenance of mouse $T_{RM}$ cells.[6,42] More recently, Runx3 and Bhlhe40 were identified as transcription factors that could regulate $T_{RM}$ cell development and functionality.[43,44]

The capacity of $T_{RM}$ cells to protect against re-infection and tumor growth has now been shown in numerous settings.[45] Using experimental systems where circulating memory T cells are depleted, leaving only tissue-resident cells, it has been shown that $T_{RM}$ cells are capable of "sounding the alarm" against recurrent immunogenic challenges.[46] Upon restimulation, $T_{RM}$ cells are capable of proliferating, secreting effector cytokines, such as interferon-γ (IFNγ), tumor necrosis factor-α (TNFα), and granzyme B, and recruiting other immune cells to the site of challenge; therefore, the mucosal recall response is contributed both by pre-existing $T_{RM}$ cells and those recruited from the circulation.[47,48] $T_{RM}$ cells prevent and control a wide variety of viral infections.[14,49–53] Additionally, $T_{RM}$ cell abundance in tumors positively correlates with patient survival,[11,54–58] and they are able to maintain malignant cells in a state of equilibrium to prevent outgrowth.[3] All the above illustrate the role of $T_{RM}$ cells as critical players in mediating long-term immunity.

## FROM MICE TO MEN: INVESTIGATING HUMAN $T_{RM}$ CELLS

The understanding of murine $T_{RM}$ cell biology has driven the investigation of $T_{RM}$ cells in an array of human conditions, including in the context of organ donation and transplantation, infectious diseases, and tumor biology. The persistence of donor HLA-mismatched $T_{RM}$ cells following facial,[59] lung[60] and small-bowel[61,62] transplantation provides strong evidence for non-recirculating $T_{RM}$ cells in human tissue. In one study, organ donors were analyzed over six decades of life, and the frequency of $CD4^+$ or $CD8^+$ T cells with a $CD69^+$ or $CD69^+CD103^+$ phenotype was found to be the greatest in mucosal sites, including the gut and lung, compared to lymphoid tissue.[63] Additionally, the administration of anti-CD52 therapeutic antibody (alemtuzumab) to patients with cutaneous T cell lymphoma was found to deplete circulating T cells, but spare those found in skin, illustrating a population of tissue-resident skin cells in disequilibrium with the blood.[64]

While CD69 expression is generally used to identify human $CD8^+$ and $CD4^+$ $T_{RM}$ cells, it is likely that additional resident T cells exist that do not express this putative marker, as has been reported in mice.[15] For example, while $CD69^+CD103^-$ and $CD69^+CD103^+$ populations of $CD8^+$ and $CD4^+$ $T_{RM}$ cells have been found in tissues, including healthy human lung[60] and skin,[65] $T_{RM}$ cells lacking the expression of both of these markers have been reported in cells from the female reproductive tract,[50,66] pancreas,[66] and salivary glands.[40,67]

Even within the same tissue, the $T_{RM}$ cell pool displays heterogeneity, with distinct transcriptional and phenotypic subsets.[23] For example, skin $CD8^+$ $T_{RM}$ cells may be $CD49a^+$ or $CD49^-$,[10] with the expression of CD49a facilitating $T_{RM}$ cell retention through its dimerization with CD29 (integrin β1) and the binding of collagen IV and laminin.[68] $CD49a^+$ $T_{RM}$ cells have a cytotoxic phenotype based on perforin and IFNγ production, while $CD49a^-$ $T_{RM}$ cells can secrete IL-17.[10,37] Given the unique microenvironment of various organs, local tissue-specific features are likely associated with the differentiation, homeostasis, and protective functions of $T_{RM}$ cells (reviewed in ref. [69]).

It has been demonstrated that the $CD69^+$ memory T cells isolated from human lung tissue share a similar transcriptional profile to that of mouse $T_{RM}$ cells, with the upregulation of the surface markers *Itgae* (which encodes CD103), *Itga1* (which encodes CD49a), and *Cxcr6* and the downregulation of migration-associated genes such as *S1pr1*, *Klf2,* and *Sell* (encodes CD62L) when compared to $CD69^-$ memory T cell compartments from the lung and spleen.[23] The expression of immune checkpoints, including PD-1,[23,48] on $T_{RM}$ cells indicates that they may be negatively regulated to prevent aberrant activation, a feature that may be critical to the tumor response following treatment with immune checkpoint inhibitors.

Despite the discovery of $T_{RM}$ cells in various human tissues, there is still a lack of complete understanding surrounding $T_{RM}$ cell identification, development, and functionality. Below, we discuss reports on human $T_{RM}$ cells with a focus on $CD8^+$ $T_{RM}$ cells in a range of disease settings, highlighting their potential to promote tissue immunity in some contexts and to contribute to tissue damage in others (summarized in Fig. 1).

## $T_{RM}$ CELLS IN INFECTIOUS DISEASES

It has been well established that classic circulating effector memory and central memory T cells ($T_{EM}$ cells and $T_{CM}$ cells, respectively) provide critical immune memory to infectious agents and protect against re-infection. Circulating naive T cells migrate through the blood and lymphoid tissue until they encounter a cognate antigen on antigen-presenting cells. This leads to cellular activation of the naïve cell, transformation into a memory T cell, and clonal expansion. A subset of $T_{EM}$ will survive the following memory T cell constriction to become $T_{CM}$ cells; these cells traffic through blood and lymph and provide an augmented effector response upon antigen re-encounter that contributes to the prevention and control of disease (reviewed in refs. [70,71]). Two phenomena well described in classic circulating T cells are memory inflation and exhaustion; however, it is unknown whether these phenomena similarly occur in $T_{RM}$ cells. Memory T cell inflation describes the development of expanded, functionally distinct antigen-specific $CD8^+$ T cells. These populations occur as the result of restricted contraction, maintain a persisting $T_{EM}$ phenotype without features of exhaustion and have been most characterized in chronic viral infections, including murine and human cytomegalovirus (CMV; reviewed in ref. [72]). The repeated antigenic stimulation that occurs in both chronic infection and malignancy leads to an induced hyporesponsiveness of antigen-specific $CD8^+$ T cells known as T cell exhaustion. The terminally differentiated exhausted T cells of chronic infection have a PD-$1^+CXCR5^-TIM3^+EOMES^{hi}TBET^{lo}$ phenotype (reviewed in ref. [73]).

More recently, the role of non-recirculating $T_{RM}$ cells in the control of infectious diseases has become appreciated. Poised in front-line niches, $T_{RM}$ cells are opportunely placed to protect against pathogen invasion. Human $T_{RM}$ cells have been most studied in the context of viral immunity, but have also been examined in a number of bacterial, parasitic, and fungal infections (reviewed in ref. [74]). Here, we review the contribution of $T_{RM}$ cells to immunity against common viral infections by summarizing evidence derived from primary human tissue and relevant animal models of disease.

### Influenza

Influenza-specific $T_{RM}$ cells have been detected in the respiratory tract of infected patients,[75–79] and these cells play a role in the control of acute infection and long-term immunity.[38] Influenza-specific $T_{RM}$ cells are highly proliferative and polyfunctional,[80] demonstrating a rapid and robust IFNγ and TNFα response upon ex vivo stimulation.[80] Prior exposure correlates with protection against re-infection,[81] possibly due to the accumulation of $CD8^+$ $T_{RM}$ cells in the lungs.[77,79] This observation has led to investigation into whether influenza-specific $T_{RM}$ cells play a role in this process and provide long-term heterosubtypic protection.[22,51,52,78,82] However, while $T_{RM}$ cells in most tissues are thought to be long

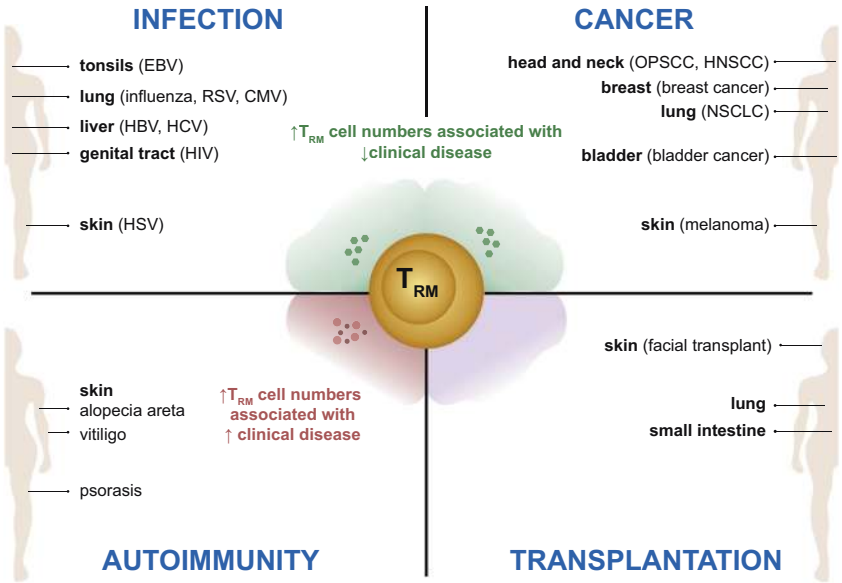


**Fig. 1 Overview of $T_{RM}$ cell function in human disease.** Human $T_{RM}$ cells have been isolated from a broad range of tissues and assessed for their associations with disease activity in the context of infection, cancer, autoimmunity and transplantation as summarized here. **Infection:** Epstein–Barr virus (EBV)-specific T cells have been identified in the tonsils of infected patients and have shown an increased frequency of CD69 and CD103 coexpression compared to their counterparts in the blood and spleen.[125–127] Lung $T_{RM}$ cells from influenza patients[195] as well as liver $T_{RM}$ cells from hepatitis B virus (HBV)-infected patients[35] are capable of producing strong levels of IFNγ and TNFα ex vivo, and high numbers of these $T_{RM}$ cells were found to correlate with reduced disease severity. This was similarly observed for patients infected with respiratory syncytial virus (RSV),[93–95] cytomegalovirus (CMV),[117,118,120–122,124] and hepatitis C virus (HCV),[35] whereby increased $T_{RM}$ cell numbers were associated with reduced disease activity. A more robust polyfunctional cytokine response by human immunodeficiency virus (HIV)-specific $T_{RM}$ cells is observed in patients who are able to better control infection.[131–135] While herpes simplex virus (HSV)-specific $T_{RM}$ cells have shown direct viral control in murine studies,[103–105] it has also been predicted that a higher density of HSV-reactive $T_{RM}$ cells in humans can correlate with successful viral containment.[108] **Cancer:** Multiple studies have demonstrated that increased numbers of $T_{RM}$ cells can correlate with an improved survival rate of patients, including those with oropharyngeal squamous cell carcinoma (OPSCC),[166–168] head and neck squamous cell carcinoma (HNSCC),[154] breast cancer,[11] nonsmall-cell lung cancer (NSCLC),[54] bladder cancer,[56,149] and melanoma.[55] Moreover, $T_{RM}$ cells with higher levels of perforin, granzyme B, and other effector proteins were noted in cohorts of patients with better disease prognosis.[11,56,149] **Autoimmunity:** The presence of cytokine-secreting $T_{RM}$ cells in the skin has been shown to be associated with poor outcomes in psoriasis,[10] vitiligo,[10] and alopecia areata (AA).[187] While an increase in IL-17 production has been correlated with psoriasis disease activity,[10] the secretion of IFNγ may be linked to AA disease progression,[187] and the production of perforin and granzyme B may play a role in vitiligo.[10] **Transplantation:** Studies have described the persistence of donor-derived lymphocytes in allografts of solid organ transplantation. While the correlation of donor-derived $T_{RM}$ cells in both intestinal[61,62] and lung[60] transplantation has been associated with a reduced incidence of rejection, conflicting studies from facial skin transplant inferred negative outcomes with the use of donor-derived $T_{RM}$ cells.[59] Therefore, the contribution of $T_{RM}$ cells to the transplantation field is still in its infancy, and more studies are needed to understand the contribution of donor and recipient cells to allograft rejection.

lived,[5,6,12] it was also recently demonstrated in a mouse model that influenza-specific lung $T_{RM}$ cells can decline during convalescence and increase their expression of apoptotic proteins.[83] It is not known whether human lung $T_{RM}$ cells decay in a similar way to mouse lung $T_{RM}$ cells or whether this contributes to the loss of heterosubtypic immunity against influenza infection. Ex vivo T cell receptor (TCR) analysis of influenza-specific clonotypes in the lung is diverse, but certain sequences can also be found in other tissues, such as blood, spleen, and lymph nodes.[84] Whether these lymphoid sites act as a source of replenishment for influenza-specific lung $T_{RM}$ cells is unknown. Certainly, it would be of value to assess whether there are preferred clonotypes that form resident and circulating memory T cells.[84] The decipherment of clones that favor residency and longevity in human lung $T_{RM}$ cells would provide useful data for vaccine design that could promote the durable protection of lung tissue from repeated exposures through the formation of a persistent influenza-specific lung $T_{RM}$ cell population.[85] Currently, live attenuated influenza vaccines (LAIVs) are utilized and have been shown to induce IFNγ-producing T cells in the blood of children and adults,[86] and in animal studies, LAIVs provide protection against infection with heterosubtypic strains.[79,87,88] While the formation of $T_{RM}$ cells has been reported in patients receiving this vaccine, more information about their protective capacity upon re-infection is required.

### Respiratory syncytial virus

Respiratory syncytial virus (RSV) is an acute respiratory infection,[89,90] and unlike influenza, natural RSV infection does not elicit complete strain-specific protection upon re-exposure.[91] It has been reported that RSV-specific $CD8^+$ T cells are enriched within the lung compared to the blood,[79] and these cells remain elevated in tracheal aspirates of children during convalescence following severe RSV infection.[92] RSV-specific lung $CD8^+$ $T_{RM}$ cells coexpress CD69 and CD103; however, they were found to have lower levels of granzyme B and perforin than their blood counterparts.[93] Higher frequencies of RSV-specific $CD8^+$ $T_{RM}$ cells in the airway correlated with reduced disease severity and viral load. Similarly, low numbers of $CD8^+$ T cells in the airway[94,95] (or an increased proportion of activated T cells in the blood) of hospitalized RSV-infected adults have been associated with more severe human RSV disease.[96] This may indicate a potential role for lung $T_{RM}$ cells to control and protect against RSV infection,[93] as has been demonstrated in animal studies.[97–100]

### Herpes simplex virus

Herpes simplex virus (HSV) types 1 and 2 are neurotropic herpesviruses that establish latency in dorsal root ganglia. HSV reactivation can be asymptomatic or manifest as painful mucocutaneous ulcerations and rarely as encephalitis.[101] Episodes of

mucocutaneous HSV reactivation are frequent, and effective immune surveillance is required to prevent overt disease.[102] The importance of $T_{RM}$ cells in the control of HSV-1 and HSV-2 reactivation is well established in animal models and human ex vivo studies. Mouse HSV-1 and HSV-2 infection studies have demonstrated that localized $T_{RM}$ cells control viral latency through noncytolytic mechanisms and control viral reactivation by readily producing effector cytokines and initiating local proliferative responses.[103–105]

In humans, HSV-specific $CD4^+$ and $CD8^+$ T cells are enriched in the female genital tract compared to the circulation,[103] and HSV-2-specific $CD8^+$ T cells accumulate adjacent to peripheral nerve endings after viral reactivation.[106] In samples from the genital tract of HSV-2-infected women, HSV-specific $CD8^+$ T cells expressed the markers of tissue residency, CD69 and CD103.[107] A mathematical model has predicted that the density of HSV-2-specific $T_{RM}$ cells in human skin is critical for successful containment of viral reactivation in cells,[108] and this has been confirmed directly in mouse HSV infection models.[48]

Cytomegalovirus

CMV infects the majority of the world's population and establishes a life-long infection; reactivated CMV can infect many organs, causing retinitis, pneumonitis, colitis, hepatitis, and/or end-organ failure.[109] A significant proportion of the host immune system is devoted to the long-term control of CMV. CMV infection in mice and humans can lead to expanded, sustained effector memory $CD8^+$ T cells through the process of memory inflation, which develops in parallel with conventional contracting central memory responses to many epitopes.[110] Single-specificity inflationary T cells can constitute up to 30% of the circulating human T cell pool[110] and have been shown to provide protection against viral challenge in mouse models.[111] Inflationary CMV-specific T cells abundantly express CX3CR1, which recognizes the fractalkine expressed by endothelial cells at intermediate ($CX3CR1^{int}$) and high levels.[112] $CX3CR1^{int}$ $CD8^+$ memory T cells (termed peripheral memory cells) are associated with enhanced self-renewal, proliferative, and tissue-surveying properties,[113] suggesting that $CX3CR1^{int}$ CMV-specific T cells may be important for the development of memory inflation.[112]

Mouse infection models have shown a clear role of CMV-specific $T_{RM}$ cells in controlling viral replication. After primary murine CMV (MCMV) infection, virus-specific $T_{RM}$ cells progressively accumulate in mucosal tissues and salivary glands,[114] with MCMV-specific $T_{RM}$ cells providing protection against local re-infection.[40] Lung MCMV-specific T cells are maintained in an antigen-independent manner and are long lived compared to effector memory cells induced by acute respiratory viral infections.[115] MCMV-specific $CD8^+$ T cells from the gut epithelium show a transcriptome closely linked to a $T_{RM}$ cell phenotype and quite distinct from that of the dominant "inflationary" memory population.[116] The capacity of CMV to induce sustained mucosal $CD8^+$ $T_{RM}$ cell responses is of interest to vaccine design, and a number of animal studies have demonstrated that intranasal vaccination with an MCMV vector can generate persistent lung $T_{RM}$ cell responses.[99,117]

CMV-specific T cells have been detected in a variety of human tissues, including lung, spleen, bone marrow, gut, and lymph nodes.[118] A discordance in the frequency of CMV-specific $CD8^+$ T cells in blood compared with tissues is frequently observed.[118–124] In the lung and spleen, a significant proportion of CMV-specific $CD8^+$ T cells express CD69 (but not CD103), whereas influenza-specific and RSV-specific memory $CD8^+$ T cells in lung tissue coexpress both CD69 and CD103.[79] TCR analysis of CMV-specific $CD8^+$ T cells revealed scant overlap between clones in paired lymph node and blood samples and that there was little clonal overlap between the effector memory T cell and central memory T cell subsets.[124] This finding indicates that human CMV-specific $CD8^+$ T cells are anatomically compartmentalized; however, their individual contribution to the control of local CMV replication is currently unknown.

Epstein–Barr virus

Epstein–Barr virus (EBV) is a highly prevalent infection that establishes life-long latency. Oropharyngeal exposure to infected saliva leads to transmission with viral replication occurring in epithelial cells and B cells and the clinical presentation of infectious mononucleosis. Following primary infection, EBV establishes latency in the circulating memory B cell pool, and cytotoxic T cells play a major role in controlling EBV-infected cells. EBV is intermittently detected in throat washings of asymptomatic carriers, which has been attributed to the reactivation of EBV in oropharyngeal lymphoid tissue, leading to a lytic oropharyngeal infection.[125] Studies have shown that EBV-specific T cells preferentially accumulate in tonsils compared to blood and spleen and that a high proportion express CD69 and CD103.[126–128] These data suggest that tonsillar $T_{RM}$ cells may play a role in controlling viral replication in oropharyngeal tissue, thereby preventing reactivation. EBV infection is also associated with a range of cancers, including B cell-derived lymphomas, T cell lymphomas, and nasopharyngeal cancer;[129] however, it is not yet known whether EBV-specific $T_{RM}$ cells contribute to the control of EBV-related oncogenesis.

Hepatotropic viruses

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses that can cause chronic infection in the liver, leading to cirrhosis and hepatocellular cancer. In contrast to acute and resolving viral infections (e.g., influenza), the immune response to chronic viral infections is a continuous effort. This requirement may lead to different characteristics of virus-specific $T_{RM}$ cells in chronic infections compared with acute infections. Higher numbers of CD69-expressing $CD8^+$ T cells were observed in the liver of patients with partial immune control of HBV and chronic HCV infection.[35,130] In HBV infection, these cells can be distinguished by high expression of the exhaustion markers PD-1 and CD39, but are capable of producing high levels of IL-2, IFNγ, and TNFα upon ex vivo stimulation with HBV epitopes.[35] Liver $T_{RM}$ cells obtained from patients with chronic HBV expressed higher levels of granzyme B than those obtained from control patients,[130] but whether this contributes to the immunopathology of cirrhosis and hepatocellular cancer is yet to be determined.

Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a chronic noncurable infection that results in acquired immunodeficiency syndrome (AIDS) if left untreated. Although combination anti-retroviral therapy has reduced the incidence of AIDS, HIV/AIDS continues to cause significant morbidity and mortality worldwide. Most HIV replication occurs in tissues, particularly mucosal and lymphoid tissue, and $CD8^+$ T cells are critical for effective immune control. $T_{RM}$ cells are generated in response to HIV infection in multiple locations, including the gastrointestinal tract, female reproductive tract, and lymphoid tissue.[131–135] HIV-specific $CD8^+$ $T_{RM}$ cells are found in high frequencies and exhibit robust polyfunctional responses in the gastrointestinal and lymphoid tissue of individuals who naturally control HIV infection ("elite controllers"), suggesting that $T_{RM}$ cells may play an important role in limiting HIV replication.[133] Because HIV is frequently transmitted through sexual intercourse, the generation of HIV-specific $T_{RM}$ cells in the genital tract through vaccination is a desirable goal. Several studies have reported success in generating genital HIV (or simian immunodeficiency virus)-specific $T_{RM}$ cells in animals,[136–138] offering hope for similar translational studies in humans.

## $T_{RM}$ CELLS IN CANCER

The immune system plays important roles in controlling and eliminating malignant cells through tumor surveillance. The

current model of the tumor immunity cycle suggests that dendritic cells loaded with tumor antigen are presented to naive $CD8^+$ T cells in the lymph node. This results in the activation and expansion of a tumor-specific $T_{EM}$ population that traffics back to tumor sites and engages in cell-mediated tumor lysis.[139] How successful tumor-specific memory $CD8^+$ T cells are in penetrating the tumor carries important prognostic value. Memory $CD8^+$ T cells that accumulate at the peripheral margins of tumors are denoted as infiltrated-excluded and are characterized as poorly immunogenic. In contrast, memory $CD8^+$ T cells that further penetrate the tumor are classified as infiltrated-inflamed and are associated with superior responses to therapy (reviewed in ref. [140]). Similar to chronic viral infection, repeated exposures of memory T cells to their cognate antigen lead to the upregulation of immune checkpoint molecules during the process of T cell exhaustion, and these cells have been successfully targeted by immune checkpoint inhibitor therapies.[141]

$T_{RM}$ cells are located in tissues where solid tumors arise, and mounting evidence indicates that $CD8^+$ $T_{RM}$ cells play a role in the inhibition of cancer progression and metastasis. The growing understanding in this field provides an opportunity to improve upon current immunotherapies for solid tumors.

Tumors have distinct microenvironments that host heterogeneous populations, including macrophages, natural killer cells, innate lymphoid cells (ILCs), IELs, γδT cells, and group 1 ILCs. Many studies have shown that a proportion of tumor-infiltrating lymphocytes (TILs) have a $T_{RM}$ cell-like phenotype, defined by surface staining and/or molecular signature.[55,142–144] For the purpose of this review, we denote these cells as "$T_{RM}$-like TILs," a population that makes up 25–75%[142] of all TILs.

In human studies, $T_{RM}$-like TILs are found in several cancers, including melanoma,[55,143,144] non-small-cell lung cancer (NSCLC);[54,145] and breast,[11,146] colorectal,[147,148] bladder,[56,149] ovarian,[57,150,151] and cervical cancer.[152] However, the *bona fide* residency of these $CD69^+CD103^+$ TILs remains to be determined. CD69 expression may be induced by cognate antigen stimulation or oxygen deprivation, and CD103 expression can be induced on circulating $CD8^+$ T cells that recognize antigen in the presence of TGFβ,[153,154] all of which are factors that are present in the tumor microenvironment. Whether the expression of CD69 and CD103 induced by the tumor microenvironment is analogous to the formation of $T_{RM}$ cells in nonmalignant tissue is an area of current investigation.

While a high proportion of total TILs is associated with improved cancer survival, the proportion of $T_{RM}$-like TILs may also be of importance (reviewed in ref. [155]). The abundance of $T_{RM}$-like TILs in the tumor epithelium positively correlates with disease-free and/or overall survival in NSCLC[54] and breast,[11] melanoma,[55] bladder,[146] ovarian,[57] and endometrial cancer.[58] Additionally, the accumulation of $T_{RM}$-like TILs has been used to predict the clinical response to immune checkpoint inhibitors.[11,55]

Although $CD103^+CD8^+$ $T_{RM}$-like TILs often have a high expression of immune checkpoint molecules, including PD-1, TIM-3, and LAG-3, in comparison with $CD103^-$ TILs, their ability to produce cytotoxic molecules and effector cytokines is maintained.[11,54,143,145,152,156] $T_{RM}$-like TILs exhibit enhanced cytotoxic potential and effector functions compared with $CD103^-$ TILs, suggesting that they potentially mediate superior tumor surveillance compared to circulating tumor-specific T cells.[157] As expected, $T_{RM}$-like TILs were capable of mediating a melanoma-immune equilibrium in mouse skin.[3] In vitro, $CD103^+$ $T_{RM}$-like TILs were more efficient at lysing NSCLC cells than their $CD103^-$ counterparts, possibly due to these cells being able to form more stable synapses with target cells and to direct cytotoxic granules in a polarized fashion.[145,158] Similarly, $CD39^+CD103^+CD8^+$ $T_{RM}$-like TILs had the highest tumor reactivity in vitro in tumor specimens obtained from patients with melanoma, lung cancer, HNSCC, ovarian cancer, and rectal cancer.[154]

A significant proportion of TILs may be $T_{RM}$-like and potentially do not recirculate, which has implications for divergent treatment responses in metastatic disease.[142] TILs are established in each metastasis early, and the TCR repertoires are distinct between individual metastatic sites. The interlesion diversity of TCRs is mostly accounted for by $T_{RM}$-like TILs,[143] even with apparent equal exposure to neoantigens. This suggests that the interlesional diversity of tissue-resident T cells may differentially affect the outcome of checkpoint inhibitor therapy at each site.[143]

A more comprehensive understanding of the characteristics of tumor-residing $T_{RM}$ cells in different cancer types may reveal novel targets for therapeutic intervention.[159] The role of $T_{RM}$-like TILs in organ-specific malignancies, as elucidated in primary human tissues and animal models of disease, is discussed further below and summarized in Fig. 1.

### Melanoma

Mouse models have provided strong evidence that $T_{RM}$ cells mediate effective antitumor responses to melanoma and suppress tumor growth,[3,160] providing a basis for translational studies in humans. Indications that $T_{RM}$ cells play a role in human melanoma are suggested from reports demonstrating improved survival in patients with greater proportions of $T_{RM}$-like TILs and the increased expression of tissue residency genes, including *Cd69*, *Itgae*, and *Cd244*.[55] $T_{RM}$-like TILs had significantly higher levels of PD-1 (~75% of $CD8^+$ T cells) than their $CD69^-CD103^-$ counterparts, and the potential significance of this observation was sustained by longitudinal data that demonstrated that these PD-$1^+CD69^+CD103^+$ T cells expand early during anti-PD-1 therapy compared to baseline values.[55] In the same study, the authors also associated the level of *Il-15* transcripts with patient outcome, where improved survival rates were directly proportional to the expression of IL-15 in the tumor.[55] While skin $T_{RM}$ cells are known to require IL-15 for their development and longevity, an evaluation of whether this cytokine in the local tumor microenvironment can directly affect $T_{RM}$-like TILs to promote cancer regression is yet to be determined. An understanding of the contribution of $T_{RM}$ cells in melanoma has the potential to direct the design of anti-melanoma vaccines for long-term protection, which has shown promise in animal models.[161]

### Non-small-cell lung cancer

NSCLC is the most common form of lung cancer[162] and is a setting in which the characterization of lung $T_{RM}$ cells is being investigated. Reports have noted the presence of tumor-specific $CD103^+$ $T_{RM}$-like TILs in NSCLC tissue, and the transcriptional signature of these cells was similar to that of infection-induced lung $T_{RM}$ cells, including a high expression of *Itgae*, *Cxcr6*, and *Ctla4* with the downregulation of *Klf2*.[54] Moreover, $T_{RM}$-like TILs had increased levels of genes associated with cell cycling, proliferation, and toxicity.[54] Patients with high proportions of TILs had reduced mortality rates, and the risk was further reduced in patients with higher proportions of $T_{RM}$-like TILs,[54] suggesting the potential cytotoxic response of lung $T_{RM}$ cells for controlling NSCLC.

### Bladder cancer

The successful use of the therapeutic intravesical bacillus Calmette-Guerin in bladder cancer demonstrates the capacity to stimulate a localized T cell-mediated antitumor response.[163] $T_{RM}$-like TILs were found in local tissue from patients with bladder urothelial cancer,[56] and these cells had high expression of perforin, granzyme B, and PD-1 compared with $CD8^+$ T cells from the peripheral blood of healthy volunteers,[149] corroborating the licensed use of anti-PD-1 and anti-PDL1 checkpoint inhibitors for the treatment of this cancer.[164] An abundance of $T_{RM}$-like TILs has been associated with improved prognosis in bladder urothelial cancer,[56] and $T_{RM}$-like TILs were the dominant T cell subset of TILs

in patients with early (stage I) disease, suggesting a role in disease control.[149] In this setting, $T_{RM}$-like TILs demonstrated a methylation of the perforin gene that was two-fold lower than that in $CD8^+$ T cells from the peripheral blood of healthy volunteers, and this was associated with a corresponding higher perforin protein expression,[149] suggesting a potential $T_{RM}$-like TIL contribution to the control of bladder cancer.

Breast cancer

A high frequency of TILs in breast cancer is a strong predictor for improved patient survival, particularly in triple-negative and HER-2-overexpressing tumors.[11] Recently, an in-depth transcriptional analysis of TILs within primary, triple-negative human breast cancer tissue was performed and demonstrated a previously unappreciated level of heterogeneity of T cell subsets within tumors.[11] Tumors with a high number of TILs contained $CD103^+CD8^+$ T cells with a $T_{RM}$-like phenotype, and these cells expressed high levels of PD-1 and effector proteins. A $CD8^+$ $T_{RM}$-like gene signature was significantly associated with improved relapse-free and overall survival following chemotherapy and provided better prognostication than CD8 expression alone.[11] These data support the notion that authentic $T_{RM}$ cells exist within tumor microenvironments and contribute to breast cancer immune surveillance.

Oropharyngeal, head and neck cancer

The recent rise in the incidence of oropharyngeal, head and neck cancers has been attributed to high-risk strains of human papilloma virus (HPV), such as HPV16.[165] Interestingly, oropharyngeal squamous cell cancer (OPSCC) that occurs independently of HPV infection has a worse prognosis than HPV-associated OPSCC, and it has been postulated that the dense infiltration of $CD4^+$ and $CD8^+$ T cells evident in the latter disease can contribute to a strong antitumor response.[166,167] HPV-specific $CD4^+$ T cells were found at a higher concentration in the pro-inflammatory tumor microenvironment of $HPV16^+$ OPSCC than in that of $HPV16^-$ OPSCC, and these cells expressed a type 1 T helper (Th1) and type 17 T helper (Th17) phenotype and high levels of CD38, PD-1, and the C-type lectin CD161.[168] Improved survival was positively associated with the proportion of $CD4^+CD161^+$ TILs as well as greater frequencies of $T_{RM}$-like TILs.[168] The expression of CD161 on $T_{RM}$ cells has been noted in the colon,[169] and while its exact function in the setting of malignancy is currently unknown, it may provide an additional correlative marker of patient outcomes.[170]

In patients with primary head and neck squamous cell carcinoma (HNSCC), a low frequency of $CD39^+CD103^+$ $CD8^+$ $T_{RM}$-like TILs was associated with more advanced disease, and those with a high frequency of $CD39^+CD103^+$ $CD8^+$ $T_{RM}$-like TILs had better survival at 3 years than those with a low frequency (86% survival versus 58%).[154] Taken together, many independent studies on diverse cancer types corroborate the consistent observation that improved patient outcomes are strongly correlated with increased frequencies of $T_{RM}$-like TILs. It is postulated that the enhanced cytotoxic and functional potential of $T_{RM}$-like TILs, compared with nonresident T cell counterparts, including the increased proficiency of tumor cell lysis, forms the basis of the reported patient survival benefits.

## $T_{RM}$ CELLS IN AUTOIMMUNITY

Recent studies indicate that $T_{RM}$ cell populations residing in the same tissue are highly heterogeneous with distinct phenotypic and functional profiles.[65,171,172] This heterogeneity is evident in human disease, and while $T_{RM}$ cells are beneficial against infection and cancer, they may also contribute to the pathology of autoimmune and inflammatory diseases.[173] While $T_{RM}$ cells have been implicated in the pathogenesis of multiple sclerosis,[174] type 1 diabetes mellitus,[175] and inflammatory bowel disease,[176] here we focus on the emerging role of pathogenic $T_{RM}$ cells in mediating common autoimmune diseases of the skin, where the evidence is the strongest[177] and has been derived both from animal models and primary human tissue (Fig. 1).

Psoriasis

The observation that psoriatic skin lesions reoccur at the same location led to speculation that $T_{RM}$ cells could be the mediator of this site-specific response.[178] The pathogenesis of psoriasis is a complex interplay of dysregulated immune cells and cytokines, including IL-17, IL-12, IFNγ, TNFα, and IL-23 (reviewed in ref. [179]). Recent investigations have focused on infiltrating $CD4^+$ and/or $CD8^+$ T cells and skin-resident T cells as the drivers of the abnormal regulation of the IL-23/IL-17 axis.[10,180] The first indication that $T_{RM}$ cells may have a role in the pathogenesis of psoriasis was the finding that the inhibition of T cell migration from the blood to the skin (by E-selectin blockade) was an ineffective treatment.[181] The transfer of nonlesional skin grafts from patients with psoriasis to immunodeficient mice resulted in psoriatic lesions on the mice, indicating that autoreactive pathogenic T cells were present in healthy-appearing skin and that psoriatic skin lesions can develop without the recruitment of cells from blood.[182] TCR gene sequencing showed that resolved psoriatic lesions retain IL-17-producing oligoclonal T cell populations, suggesting a mechanism by which disease can reoccur at the same site.[183] Subsequent studies demonstrated that IL-22-secreting $CD4^+$ T cells and IL-17-secreting $CD8^+$ T cells remained resident in healed psoriatic skin after treatment with a number of therapies.[183,184] Furthermore, the lack of CD49a expression on $CD8^+$ $T_{RM}$ cells from psoriasis lesions defines a $T_{RM}$ cell subset producing IL-17.[10] Biological treatments targeting TNFα, IL-17, or IL-23 have revolutionized the treatment of psoriasis and have helped to demonstrate the centrality of T cells to the disorder.[178] It is currently unknown whether $T_{RM}$ cells directly contribute to the exacerbation of psoriasis, and the determination of whether $T_{RM}$ cell-mediated cytokine secretion plays a role in disease pathogenesis may encourage the advent of novel therapies aimed at dislodging pathogenic $T_{RM}$ cells while preserving protective counterparts.

Alopecia areata

Alopecia areata (AA) is a chronic immune-mediated disease that results in nonscarring hair loss.[185] The pathogenesis of AA is only partially understood, but it is thought that genetic and environmental factors cause an autoimmune reaction in hair follicles.[186] MHC class II is normally absent in hair follicle root sheaths and hair matrix, but increased MHC class II expression and the upregulation of adhesion molecules occurs in AA.[187] Skin Th1 cells produce IFNγ, which triggers the infiltration of cytotoxic $CD8^+$ T cells to the perifollicular area, leading to hair cycle arrest.[187] Early evidence that skin $T_{RM}$ cells may play a pathogenic role in AA was suggested by a study in which T cells isolated from AA scalp explants were injected into severe combined immunodeficiency (SCID) mice, and hair growth and clinical parameters were monitored. When compared to mice that had not received T cells (or had been injected with peripheral blood mononuclear cells), mice with AA skin-derived T cells demonstrated hair loss as a result of fewer hair follicles and presented histological evidence of AA.[188] Transcriptional profiling of AA skin revealed gene signatures suggestive of cytotoxic effector $CD8^+$ T cells[187] and higher transcripts of *Itgae*.[189] Inhibitors of the Janus kinase (JAK) signaling pathway (e.g., tofacitinib), which predominantly produces IFNγ, have shown promise in treating AA.[190] Lesional T cell clones do not completely disappear after tofacitinib administration,[191] leading to the relapse of disease after treatment cessation. However, it is yet to be confirmed whether $T_{RM}$ cells are the main source of IFNγ in AA and (if so) the effect of tofacitinib on $T_{RM}$ cell functionality.

### Vitiligo

Vitiligo is a disease characterized by the apoptosis of melanocytes or the lack of melanin production, which results in depigmented skin.[192] $CD8^+$ $T_{RM}$ cells expressing the cytotoxic molecules perforin and granzyme B are present in the skin of active and stable vitiligo lesions and are responsive to IL-15 stimulation,[10] a cytokine with a role in $T_{RM}$ development and survival in skin.[7] Both human and mouse $T_{RM}$ cells express the CD122 subunit of the IL-15 receptor, and keratinocytes upregulate CD215, the subunit required to display the cytokine on their surface to promote the activation of T cells.[193] In mice, the targeting of IL-15 signaling with an anti-CD122 antibody reversed vitiligo, and the effects of such treatment remain to be confirmed in humans.[193] Further work is also needed to determine whether the ablation of IL-15 signaling in $T_{RM}$ cells can directly affect disease outcomes in vitiligo.

## $T_{RM}$ CELLS IN TRANSPLANTATION

Donor-derived lymphocytes are transferred within the allograft during solid organ transplantation. The close association between donor-derived $T_{RM}$ cells and host cells may determine whether allografts undergo acute or chronic rejection (Fig. 1).[59,194,195] It has been shown that donor-derived $CD4^+$ and $CD8^+$ IELs were dominant in an intestinal allograft for ~400 days post transplant, after which recipient-derived T cells (which adopted a $T_{RM}$ cell phenotype) then outnumbered donor-derived cells.[61,62] During rejection, host-versus-graft reactive T cell clones accumulated in the graft, and the infiltration of recipient T cells was accelerated and was associated with a reduced proportion of donor-derived cells. However, in the absence of overwhelming cellular and antibody-mediated rejection, donor-derived $T_{RM}$ cells persisted and even expanded in the graft, delaying complete repopulation by recipient T cells and possibly reducing the risk of rejection.[61]

While the persistence of donor-derived $T_{RM}$ cells has been associated with a reduced incidence of rejection in both intestinal[61] and lung[60] transplants, $T_{RM}$ cells have conversely also been implicated in driving allograft rejection. Following a facial transplant, donor-derived $CD8^+$ T cells were predominantly skin-resident ($CD8^+$ $CD69^+CD103^+CLA^+$) phenotypes, and histological analysis revealed that these donor cells were associated with areas of damaged vasculature and epithelium.[59] The results of this report suggest that donor-derived T cells may also play a role in tissue injury that results in graft rejection. Overall, the contribution of tissue-resident cells to the field of transplantation is in its infancy, and more studies are needed to clarify the contribution of $T_{RM}$ cells to graft rejection and stability.

## CONCLUDING REMARKS AND FUTURE DIRECTIONS

The importance of human $T_{RM}$ cells is increasingly recognized in a wide array of tissue-specific diseases. Progress has been made in identifying surface markers and transcriptional profiles of human $T_{RM}$ cells, although unique human $T_{RM}$ cell phenotypes and signatures still remain to be elucidated. Human studies have shown the beneficial roles of $T_{RM}$ cells in controlling infections, and $T_{RM}$ cells are being targeted in the rational design of T cell vaccines. Additionally, $T_{RM}$ cells appear to play an important role in the control of malignancies and will prove a likely target of cancer immunotherapies. However, given the potentially harmful contribution of $T_{RM}$ cells in autoimmune diseases, understanding both the protective and pathogenic human $T_{RM}$ cell roles is crucial for the safe design of approaches that allow for their manipulation. Many critical questions remain to be answered. For example, do $T_{RM}$ cells contribute to pathology in a direct or indirect manner? What signaling pathways regulate $T_{RM}$ cell differentiation and longevity? How can these processes be manipulated to enhance or eliminate $T_{RM}$ cells in a tissue-specific manner? Much work is required to understand the breadth of $T_{RM}$ cell heterogeneity and function in human tissues, such that adverse effects can be predicted and controlled for; however, there appears enormous potential to harness $T_{RM}$ cells for novel T cell-based vaccines and immunotherapies for a broad range of diseases.

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## ADDITIONAL INFORMATION

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## REFERENCES

1. Mackay, L. & Kallies, A. Transcriptional regulation of tissue-resident lymphocytes. *Trends Immunol.* **38**, 94–103 (2017).
2. Mueller, S. & Mackay, L. Tissue-resident memory T cells: local specialists in immune defence. *Nat. Rev. Immunol.* **16**, 79–89 (2016).
3. Park, S. L. et al. Tissue-resident memory CD8+ T cells promote melanoma–immune equilibrium in skin. *Nature* **565**, 366–371 (2019).
4. Masopust, D., Vezys, V., Marzo, A. & Lefrancois, L. Preferential localization of effector memory cells in nonlymphoid tissue. *Science* **291**, 2413 (2001).
5. Gebhardt, T. et al. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat. Immunol.* **10**, 524–530 (2009).
6. Mackay, L. et al. The developmental pathway for CD103(+)CD8+ tissue-resident memory T cells of skin. *Nat. Immunol.* **14**, 1294–1301 (2013).
7. Mackay, L. et al. T-box transcription factors combine with the cytokines TGF-beta and IL-15 to control tissue-resident memory T cell fate. *Immunity* **43**, 1101–1111 (2015).
8. Schenkel, J. M. et al. IL-15-independent maintenance of tissue-resident and boosted effector memory CD8 T cells. *J. Immunol.* **196**, 3920–3926 (2016).
9. Sathaliyawala, T. et al. Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. *Immunity* **38**, 187–197 (2013).
10. Cheuk, S. et al. CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin. *Immunity* **46**, 287–300 (2017).
11. Savas, P. et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. *Nat. Med* **24**, 986–993 (2018).
12. Masopust, D. et al. Dynamic T cell migration program provides resident memory within intestinal epithelium. *J. Exp. Med.* **207**, 553–564 (2010).
13. Klonowski, K. D. et al. Dynamics of blood-borne CD8 memory T cell migration in vivo. *Immunity* **20**, 551–562 (2004).
14. Jiang, X. et al. Skin infection generates non-migratory memory CD8+ T(RM) cells providing global skin immunity. *Nature* **483**, 227–231 (2012).
15. Steinert, E. et al. Quantifying memory CD8 T cells reveals regionalization of immunosurveillance. *Cell* **161**, 737–749 (2015).
16. Anderson, K. et al. Cutting edge: intravascular staining redefines lung CD8 T cell responses. *J. Immunol.* **189**, 2702–2706 (2012).
17. Vesely, M. et al. Effector TH17 cells give rise to long-lived TRM cells that are essential for an immediate response against bacterial infection. *Cell* **178**, 1176–1188.e15 (2019).
18. Iijima, N. & Iwasaki, A. T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. *Science* **346**, 93–98 (2014).
19. Hondowicz, B. D. et al. Interleukin-2-dependent allergen-specific tissue-resident memory cells drive asthma. *Immunity* **44**, 155–166 (2016).
20. Collins, N. et al. Skin CD4(+) memory T cells exhibit combined cluster-mediated retention and equilibration with the circulation. *Nat. Commun.* **7**, 11514 (2016).
21. Beura, L. K. et al. CD4+ resident memory T cells dominate immunosurveillance and orchestrate local recall responses. *J. Exp. Med.* **216**, jem.20181365 (2019).
22. Teijaro, J. et al. Cutting edge: tissue-retentive lung memory CD4 T cells mediate optimal protection to respiratory virus infection. *J. Immunol.* **187**, 5510 (2011).
23. Kumar, B. et al. Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. *Cell Rep.* **20**, 2921–2934 (2017).
24. Oja, A. et al. Trigger-happy resident memory CD4(+) T cells inhabit the human lungs. *Mucosal Immunol.* **11**, 654–667 (2018).
25. Kleinschek, M. A. et al. Circulating and gut-resident human Th17 cells express CD161 and promote intestinal inflammation. *J. Exp. Med.* **206**, 525–534 (2009).

26. Wakim, L. et al. The molecular signature of tissue resident memory CD8 T cells isolated from the brain. *J. Immunol.* **189**, 3462–3471 (2012).
27. Skon, C. et al. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory CD8+ T cells. *Nat. Immunol.* **14**, 1285–1293 (2013).
28. Mandala, S. et al. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. *Science* **296**, 346–349 (2002).
29. Mackay, L. et al. Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. *J. Immunol.* **194**, 2059–2063 (2015).
30. Ma, C., Mishra, S., Demel, E. L., Liu, Y. & Zhang, N. TGF-β controls the formation of kidney-resident T cells via promoting effector T cell extravasation. *J. Immunol.* **198**, 749–756 (2017).
31. Mackay, L. et al. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science* **352**, 459–463 (2016).
32. Fernandez-Ruiz, D. et al. Liver-resident memory CD8+ T cells form a front-line defense against malaria liver-stage infection. *Immunity* **45**, https://doi.org/10.1016/j.immuni.2016.08.011 (2016).
33. Bergsbaken, T. & Bevan, M. Proinflammatory microenvironments within the intestine regulate the differentiation of tissue-resident CD8(+) T cells responding to infection. *Nat. Immunol.* **16**, 406–414 (2015).
34. Sheridan, B. et al. Oral infection drives a distinct population of intestinal resident memory CD8(+) T cells with enhanced protective function. *Immunity* **40**, 747–757 (2014).
35. Pallett, L. et al. IL-2(high) tissue-resident T cells in the human liver: sentinels for hepatotropic infection. *J. Exp. Med.* **214**, 1567 (2017).
36. Kumar, B. V. et al. Functional heterogeneity of human tissue-resident memory T cells based on dye efflux capacities. *JCI Insight* **3**, e123568 (2018).
37. Hombrink, P. et al. Programs for the persistence, vigilance and control of human CD8(+) lung-resident memory T cells. *Nat. Immunol.* **17**, 1467–1478 (2016).
38. Pizzolla, A. & Wakim, L. M. Memory T cell dynamics in the lung during influenza virus infection. *J. Immunol.* **202**, 374–381 (2019).
39. Smith, C. J., Caldeira-Dantas, S., Turula, H. & Snyder, C. M. Murine CMV infection induces the continuous production of mucosal resident T cells. *Cell Rep.* **13**, 1137–1148 (2015).
40. Thom, J., Weber, T., Walton, S., Torti, N. & Oxenius, A. The salivary gland acts as a sink for tissue-resident memory CD8+ T cells, facilitating protection from local cytomegalovirus infection. *Cell Rep.* **13**, 1125 (2015).
41. Zhang, N. & Bevan, M. J. Transforming growth factor-β signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. *Immunity* **39**, 687–696 (2013).
42. Zaid, A. et al. Persistence of skin-resident memory T cells within an epidermal niche. *Proc. Natl Acad. Sci. USA* **111**, 5307–5312 (2014).
43. Milner, J. et al. Runx3 programs CD8(+) T cell residency in non-lymphoid tissues and tumours. *Nature* **552**, 253–257 (2017).
44. Li, C. et al. The Transcription factor Bhlhe40 programs mitochondrial regulation of resident CD8+ T cell fitness and functionality. *Immunity* **51**, 491–507.e7 (2019).
45. Masopust, D. & Soerens, A. G. Tissue-resident T cells and other resident leukocytes. *Annu. Rev. Immunol.* **37**, 1–26 (2019).
46. Schenkel, J., Fraser, K. A., Vezys, V. & Masopust, D. Sensing and alarm function of resident memory CD8+ T cells. *Nat. Immunol.* **14**, 509 (2013).
47. Beura, L. K. et al. Intravital mucosal imaging of CD8+ resident memory T cells shows tissue-autonomous recall responses that amplify secondary memory. *Nat. Immunol.* **19**, 173–182 (2018).
48. Park, S. et al. Local proliferation maintains a stable pool of tissue-resident memory T cells after antiviral recall responses. *Nat. Immunol.* **19**, 183–191 (2018).
49. Mackay, L. et al. Long-lived epithelial immunity by tissue-resident memory T (TRM) cells in the absence of persisting local antigen presentation. *Proc. Natl Acad. Sci. USA* **109**, 7037–7042 (2012).
50. Shin, H. & Iwasaki, A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. *Nature* **491**, 463 (2012).
51. Pizzolla, A. et al. Resident memory CD8+ T cells in the upper respiratory tract prevent pulmonary influenza virus infection. *Sci. Immunol.* **2**, eaam6970 (2017).
52. Wu, T. et al. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. *J. Leukoc. Biol.* **95**, 215–224 (2014).
53. Liu, L. et al. Epidermal injury and infection during poxvirus immunization is crucial for the generation of highly protective T cell–mediated immunity. *Nat. Med.* **16**, 224 (2010).
54. Ganesan, A. et al. Tissue-resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. *Nat. Immunol.* **18**, 940–950 (2017).
55. Edwards, J. et al. CD103(+) tumor-resident CD8(+) T cells are associated with improved survival in immunotherapy-naive melanoma patients and expand significantly during anti-PD-1 treatment. *Clin. Cancer Res.* **24**, 3036–3045 (2018).
56. Wang, B. et al. CD103+ tumor infiltrating lymphocytes predict a favorable prognosis in urothelial cell carcinoma of the bladder. *J. Urology* **194**, 556–562 (2015).
57. Bösmüller, H.-C. et al. Combined immunoscore of CD103 and CD3 identifies long-term survivors in high-grade serous ovarian cancer. *Int. J. Gynecol. Cancer* **26**, 671–679 (2016).
58. Workel, H. H. et al. CD103 defines intraepithelial CD8+ PD1+ tumour-infiltrating lymphocytes of prognostic significance in endometrial adenocarcinoma. *Eur. J. Cancer* **60**, 1–11 (2016).
59. Lian, C. et al. Biomarker evaluation of face transplant rejection: association of donor T cells with target cell injury. *Mod. Pathol.* **27**, 788–799 (2014).
60. Snyder, M. E. et al. Generation and persistence of human tissue-resident memory T cells in lung transplantation. *Sci. Immunol.* **4**, eaav5581 (2019).
61. Zuber, J. et al. Bidirectional intragraft alloreactivity drives the repopulation of human intestinal allografts and correlates with clinical outcome. *Sci. Immunol.* **1**, eaah3732 (2016).
62. Bartolomé-Casado, R. et al. Resident memory CD8 T cells persist for years in human small intestine. *J. Exp. Med.* https://doi.org/10.1084/jem.20190414 (2019).
63. Thome, J. et al. Spatial map of human T cell compartmentalization and maintenance over decades of life. *Cell* **159**, 814–828 (2014).
64. Clark, R. et al. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. *Sci. Transl. Med.* **4**, 117ra7 (2012).
65. Watanabe, R. et al. Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. *Sci. Transl. Med.* **7**, 279ra39–279ra39 (2015).
66. Casey, K. A. et al. Antigen-independent differentiation and maintenance of effector-like resident memory T cells in tissues. *J. Immunol.* **188**, 4866–4875 (2012).
67. Hofmann, M. & Pircher, H. E-cadherin promotes accumulation of a unique memory CD8 T-cell population in murine salivary glands. *Proc. Natl Acad. Sci. USA* **108**, 16741–16746 (2011).
68. Topham, D. & Reilly, E. Tissue-resident memory CD8(+) T cells: from phenotype to function. *Front. Immunol.* **9**, 515 (2018).
69. Liu, Y., Ma, C. & Zhang, N. Tissue-specific control of tissue-resident memory T cells. *Crit. Rev. Immunol.* **38**, 79–103 (2018).
70. Wherry, E. & Ahmed, R. Memory CD8 T-cell differentiation during viral infection. *J. Virol.* **78**, 5535–5545 (2004).
71. Remakus, S. & Sigal, L. J. Advances in experimental medicine and biology. *Adv. Exp. Med. Biol.* **785**, 77–86 (2013).
72. Klenerman, P. The (gradual) rise of memory inflation. *Immunol. Rev.* **283**, 99–112 (2018).
73. Philip, M. & Schietinger, A. Heterogeneity and fate choice: T cell exhaustion in cancer and chronic infections. *Curr. Opin. Immunol.* **58**, 98–103 (2019).
74. Muruganandah, V., Sathkumara, H. D., Navarro, S. & Kupz, A. A systematic review: the role of resident memory T cells in infectious diseases and their relevance for vaccine development. *Front. Immunol.* **9**, 1574 (2018).
75. de Bree, G. et al. Characterization of CD4+ memory T cell responses directed against common respiratory pathogens in peripheral blood and lung. *J. Infect. Dis.* **195**, 1718 (2007).
76. Piet, B. et al. CD8(+) T cells with an intraepithelial phenotype upregulate cytotoxic function upon influenza infection in human lung. *J. Clin. Investig.* **121**, 2254 (2011).
77. Turner, D. et al. Lung niches for the generation and maintenance of tissue-resident memory T cells. *Mucosal Immunol.* **7**, 501 (2014).
78. Koutsakos, M. et al. Human CD8+ T cell cross-reactivity across influenza A, B and C viruses. *Nat. Immunol.* **20**, 613–625 (2019).
79. de Bree, G. J. et al. Selective accumulation of differentiated CD8+ T cells specific for respiratory viruses in the human lung. *J. Exp. Med.* **202**, 1433–1442 (2005).
80. Pizzolla, A. et al. Influenza-specific lung-resident memory T cells are proliferative and polyfunctional and maintain diverse TCR profiles. *J. Clin. Investig.* **128**, 721 (2018).
81. Sridhar, S. et al. Cellular immune correlates of protection against symptomatic pandemic influenza. *Nat. Med.* **19**, nm.3350 (2013).
82. Zens, K., Chen, J. & Farber, D. Vaccine-generated lung tissue-resident memory T cells provide heterosubtypic protection to influenza infection. *J. Clin. Invest. Insight* **1**, e85832 (2016).
83. Slutter, B. et al. Dynamics of influenza-induced lung-resident memory T cells underlie waning heterosubtypic immunity. *Sci. Immunol.* **2**, eaag2031 (2017).
84. Sant, S. et al. Single-cell approach to influenza-specific CD8(+) T cell receptor repertoires across different age groups, tissues, and following influenza virus infection. *Front. Immunol.* **9**, 1453 (2018).

85. Clemens, E., van de Sandt, C., Wong, S., Wakim, L. & Valkenburg, S. Harnessing the power of T cells: the promising hope for a universal influenza vaccine. *Vaccines (Basel)* **6**, E18 (2018).
86. He, X.-S. et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. *J. Virol.* **80**, 11756–11766 (2006).
87. Cheng, X. et al. Evaluation of the humoral and cellular immune responses elicited by the live attenuated and inactivated influenza vaccines and their roles in heterologous protection in ferrets. *J. Infect. Dis.* **208**, 594 (2013).
88. Jang, Y. et al. Cold-adapted X-31 live attenuated 2009 pandemic H1N1 influenza vaccine elicits protective immune responses in mice and ferrets. *Vaccine* **31**, 1320 (2013).
89. Sommer, C., Resch, B. & Simoes, E. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. *Open Microbiol. J.* **5**, 144 (2011).
90. Falsey, A., Hennessey, P., Formica, M., Cox, C. & Walsh, E. Respiratory syncytial virus infection in elderly and high-risk adults. *N. Engl. J. Med.* **352**, 1749 (2005).
91. Habibi, JozwikA. et al. Impaired antibody-mediated protection and defective IgA B-cell memory in experimental infection of adults with respiratory syncytial virus. *Am. J. Respir. Crit. Care Med.* **191**, 1040 (2015).
92. Heidema, J. et al. CD8+ T cell responses in bronchoalveolar lavage fluid and peripheral blood mononuclear cells of infants with severe primary respiratory syncytial virus infections. *J. Immunol. (Baltim., Md: 1950)* **179**, 8410 (2007).
93. Jozwik, A. et al. RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. *Nat. Commun.* **6**, 10224 (2015).
94. Cannon, M., Openshaw, P. & Askonas Cytotoxic T cells clear virus but augment lung pathology in mice infected with respiratory syncytial virus. *J. Exp. Med.* **168**, 1163 (1988).
95. Alwan, W., Record, F. & Openshaw, P. CD4+ T cells clear virus but augment disease in mice infected with respiratory syncytial virus. Comparison with the effects of CD8+ T cells. *Clin. Exp. Immunol.* **88**, 527 (1992).
96. Walsh, E. E., Peterson, D. R., Kalkanoglu, A. E., Lee, F. & Falsey, A. R. Viral shedding and immune responses to respiratory syncytial virus infection in older adults. *J. Infect. Dis.* **207**, 1424–1432 (2013).
97. Li, H. et al. Respiratory syncytial virus elicits enriched CD8+ T lymphocyte responses in lung compared with blood in African green monkeys. *PLoS ONE* **12**, e0187642 (2017).
98. Kinnear, E. et al. Airway T cells protect against RSV infection in the absence of antibody. *Mucosal. Immunol.* **11**, 290 (2018).
99. Morabito, K. et al. Intranasal administration of RSV antigen-expressing MCMV elicits robust tissue-resident effector and effector memory CD8+ T cells in the lung. *Mucosal Immunol.* **10**, 545–554 (2017).
100. Zhang, L. et al. CpG in combination with an inhibitor of notch signaling suppresses formalin-inactivated respiratory syncytial virus-enhanced airway hyperresponsiveness and inflammation by inhibiting Th17 memory responses and promoting tissue-resident memory cells in lungs. *J. Virol.* **91**, e021111-16 (2017).
101. Whitley, R. J. & Roizman, B. Herpes simplex virus infections. *Lancet* **357**, 1513–1518 (2001).
102. Mark, K. E. et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J. Infect. Dis.* **198**, 1141–1149 (2008).
103. Koelle, D. M., Abbo, H., Peck, A., Ziegweid, K. & Corey, L. Direct recovery of herpes simplex virus (HSV)-specific T lymphocyte clones from recurrent genital HSV-2 lesions. *J. Infect. Dis.* **169**, 956–961 (1994).
104. Knickelbein, J. E. et al. Noncytotoxic lytic granule–mediated CD8+ T cell inhibition of HSV-1 reactivation from neuronal latency. *Science* **322**, 268–271 (2008).
105. Wakim, L. M., Gebhardt, T., Heath, W. R. & Carbone, F. R. Cutting edge: local recall responses by memory T cells newly recruited to peripheral nonlymphoid tissues. *J. Immunol.* **181**, 5837–5841 (2008).
106. Zhu, J. et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. *J. Exp. Med.* **204**, 595–603 (2007).
107. Posavad, C. et al. Enrichment of herpes simplex virus type 2 (HSV-2) reactive mucosal T cells in the human female genital tract. *Mucosal Immunol.* **10**, 1259 (2017).
108. Schiffer, J. T. et al. A fixed spatial structure of CD8+ T cells in tissue during chronic HSV-2 infection. *J. Immunol. (Balt. Md., 1950)* **201**, 1522–1535 (2018).
109. Kotton, C. CMV: prevention, diagnosis and therapy. *Am. J. Transpl.* **13**, 24–40 (2013).
110. Karrer, U. et al. Memory inflation: continuous accumulation of antiviral CD8 + T cells over time. *J. Immunol.* **170**, 2022–2029 (2003).
111. Baumann, N. S. et al. Early primed KLRG1- CMV-specific T cells determine the size of the inflationary T cell pool. *PLos Pathog.* **15**, e1007785 (2019).
112. Gordon, C. et al. Induction and maintenance of CX3CR1-intermediate peripheral memory CD8 + T cells by persistent viruses and vaccines. *Cell Rep.* **23**, 768–782 (2018).
113. Gerlach, C. et al. The chemokine receptor CX3CR1 defines three antigen-experienced CD8 T cell subsets with distinct roles in immune surveillance and homeostasis. *Immunity* **45**, 1270–1284 (2016).
114. Smith, C., Caldeira-Dantas, S., Turula, H. & Snyder, C. Murine CMV infection induces the continuous production of mucosal resident T cells. *Cell Rep.* **13**, 1137 (2015).
115. Baumann, N. S. et al. Tissue maintenance of CMV-specific inflationary memory T cells by IL-15. *PLos Pathog.* **14**, e1006993 (2018).
116. Highton, A. J. et al. Single-cell transcriptome analysis of CD8+ T-cell memory inflation. *Wellcome Open Res.* **4**, 78 (2019).
117. Morabito, K. M. et al. Memory inflation drives tissue-resident memory CD8+ T cell maintenance in the lung after intranasal vaccination with murine cytomegalovirus. *Front. Immunol.* **9**, 1861 (2018).
118. Gordon, C. L. et al. Tissue reservoirs of antiviral T cell immunity in persistent human CMV infection. *J. Exp. Med.* **214**, jem.20160758 (2017).
119. Ward, S. M. et al. Virus-specific CD8+ T lymphocytes within the normal human liver. *Eur. J. Immunol.* **34**, 1526–1531 (2004).
120. Remmerswaal, E. B. et al. Human virus-specific effector-type T cells accumulate in blood but not in lymph nodes. *Blood* **119**, 1702–1712 (2012).
121. Letsch, A. et al. CMV-specific central memory T cells reside in bone marrow. *Eur. J. Immunol.* **37**, 3063–3068 (2007).
122. Palendira, U. et al. Selective accumulation of virus-specific CD8+ T cells with unique homing phenotype within the human bone marrow. *Blood* **112**, 3293–3302 (2008).
123. Akulian, J., Pipeling, M., John, E., Orens, J. & Lechtzin, N. High-quality CMV-specific CD4+ memory is enriched in the lung allograft and is associated with mucosal viral control. *Am. J. Transpl.* **13**, 146–156 (2013).
124. Remmerswaal, E. B. et al. Clonal evolution of CD8+ T cell responses against latent viruses: relationship among phenotype, localization, and function. *J. Virol.* **89**, 568–580 (2015).
125. Sitki-Green, D., Covington, M. & Raab-Traub, N. Compartmentalization and transmission of multiple Epstein–Barr virus strains in asymptomatic carriers. *J. Virol.* **77**, 1840–1847 (2003).
126. Woon, H. et al. Compartmentalization of total and virus-specific tissue-resident memory CD8+ T cells in human lymphoid organs. *PLoS Pathog.* **12**, e1005799 (2016).
127. Woodberry, T. et al. αEβ7 (CD103) expression identifies a highly active, tonsil-resident effector-memory CTL population. *J. Immunol.* **175**, 4355–4362 (2005).
128. Hislop, A. D. et al. Tonsillar homing of Epstein–Barr virus–specific CD8+ T cells and the virus–host balance. *J. Clin. Invest.* **115**, 2546–2555 (2005).
129. Shannon-Lowe, C. & Rickinson, A. The global landscape of EBV-associated tumors. *Front. Oncol.* **9**, 713 (2019).
130. Stelma, F. et al. Human intrahepatic CD69 + CD8+ T cells have a tissue resident memory T cell phenotype with reduced cytolytic capacity. *Sci. Rep. (UK)* **7**, 6172 (2017).
131. Gibbs, A. et al. HIV-infected women have high numbers of CD103-CD8+ T cells residing close to the basal membrane of the ectocervical epithelium. *J. Infect. Dis.* https://doi.org/10.1093/infdis/jix661 (2017).
132. Buggert, M. et al. Identification and characterization of HIV-specific resident memory CD8+ T cells in human lymphoid tissue. *Sci. Immunol.* **3**, eaar4526 (2018).
133. Kiniry, B. E. et al. Detection of HIV-1-specific gastrointestinal tissue resident CD8+ T-cells in chronic infection. *Mucosal Immunol.* **11**, 909 (2017).
134. Moylan, D. C. et al. Diminished CD103 (aEb7) expression on resident T cells from the female genital tract of HIV-positive women. *Pathog. Immun.* **1**, 371–389 (2016).
135. Damouche, A. et al. High proportion of PD-1-expressing CD4+ T cells in adipose tissue constitutes an immunomodulatory microenvironment that may support HIV persistence. *Eur. J. Immunol.* **47**, 2113–2123 (2017).
136. Tan, H.-X. et al. Induction of vaginal-resident HIV-specific CD8 T cells with mucosal prime–boost immunization. *Mucosal Immunol.* **11**, 994 (2017).
137. Zaric, M. et al. Long-lived tissue resident HIV-1 specific memory CD8+ T cells are generated by skin immunization with live virus vectored microneedle arrays. *J. Control Rel.* **268**, 166–175 (2017).
138. Adnan, S. et al. Persistent low-level replication of SIVΔnef drives maturation of antibody and CD8 T cell responses to induce protective immunity against vaginal SIV infection. *PLoS Pathog.* **12**, e1006104 (2016).
139. Chen, D. S. & Mellman, I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* **39**, 1–10 (2013).
140. Farhood, B., Najafi, M. & Mortezaee, K. CD8 + cytotoxic T lymphocytes in cancer immunotherapy: a review. *J. Cell Physiol.* **234**, 8509–8521 (2018).

141. Ribas, A. & Wolchok, J. D. Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350–1355 (2018).
142. Dhodapkar, K. Role of tissue-resident memory in intra-tumor heterogeneity and response to immune checkpoint blockade. *Front Immunol.* **9**, 1655 (2018).
143. Boddupalli, C. et al. Interlesional diversity of T cell receptors in melanoma with immune checkpoints enriched in tissue-resident memory T cells. *JCI Insight* **1**, e88955 (2016).
144. Salerno, E. P., Olson, W. C., Imming, C., Shea, S. & Slingluff, C. L. T cells in the human metastatic melanoma microenvironment express site-specific homing receptors and retention integrins. *Int. J. Cancer* **134**, 563–574 (2014).
145. Djenidi, F. et al. CD8+CD103+ tumor-infiltrating lymphocytes are tumor-specific tissue-resident memory T cells and a prognostic factor for survival in lung cancer patients. *J. Immunol.* **194**, 3475–3486 (2015).
146. Wang, Z.-Q. et al. CD103 and intratumoral immune response in breast cancer. *Clin. Cancer Res.* **22**, clincanres.0732.2016 (2016).
147. Quinn, E., Hawkins, N., Yip, Y., Suter, C. & Ward, R. CD103+ intraepithelial lymphocytes—a unique population in microsatellite unstable sporadic colorectal cancer. *Eur. J. Cancer* **39**, 469–475 (2003).
148. de Vries, N. L. et al. High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity. *Gut* gutjnl-2019-318672 (2019).
149. Hartana, C. et al. Tissue-resident memory T cells are epigenetically cytotoxic with signs of exhaustion in human urinary bladder cancer. *Clin. Exp. Immunol.* **194**, 39–53 (2018).
150. Webb, J. R. et al. Profound elevation of CD8+ T cells expressing the intraepithelial lymphocyte marker CD103 (αE/β7 Integrin) in high-grade serous ovarian cancer. *Gynecol. Oncol.* **118**, 228–236 (2010).
151. Webb, J., Milne, K. & Nelson, B. Location, location, location: CD103 demarcates intraepithelial, prognostically favorable CD8(+) tumor-infiltrating lymphocytes in ovarian cancer. *Oncoimmunology* **3**, e27668 (2014).
152. Komdeur, F. L. et al. CD103+ tumor-infiltrating lymphocytes are tumor-reactive intraepithelial CD8+ T cells associated with prognostic benefit and therapy response in cervical cancer. *Oncoimmunology* **6**, e1338230 (2017).
153. Floc'h, A. et al. αEβ7 integrin interaction with E-cadherin promotes antitumor CTL activity by triggering lytic granule polarization and exocytosis. *J. Exp. Med.* **204**, 559–570 (2007).
154. Duhen, T. et al. Co-expression of CD39 and CD103 identifies tumor-reactive CD8 T cells in human solid tumors. *Nat. Commun.* **9**, 2724 (2018).
155. Molodtsov, A. & Turk, M. Tissue resident CD8 memory T cell responses in cancer and autoimmunity. *Front. Immunol.* **9**, 2810 (2018).
156. Clarke, J. et al. Single-cell transcriptomic analysis of tissue-resident memory T cells in human lung cancer. *J. Exp. Med*. https://doi.org/10.1084/jem.20190249 (2019).
157. Park, S. L., Gebhardt, T. & Mackay, L. K. Tissue-resident memory T cells in cancer immunosurveillance. *Trends Immunol.* **40**, 735–747 (2019).
158. Franciszkiewicz, K. et al. CD103 or LFA-1 engagement at the immune synapse between cytotoxic T cells and tumor cells promotes maturation and regulates T-cell effector functions. *Cancer Res.* **73**, 617–628 (2013).
159. Amsen, D., van Gisbergen, K., Hombrink, P. & van Lier, R. Tissue-resident memory T cells at the center of immunity to solid tumors. *Nat. Immunol.* **19**, 538–546 (2018).
160. Malik, B. et al. Resident memory T cells in the skin mediate durable immunity to melanoma. *Sci. Immunol.* **2**, eaam6346 (2017).
161. Galvez-Cancino, F. et al. Vaccination-induced skin-resident memory CD8(+) T cells mediate strong protection against cutaneous melanoma. *Oncoimmunology* **7**, e1442163 (2018).
162. Molina, J. R., Yang, P., Cassivi, S. D., Schild, S. E. & Adjei, A. A. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin. Proc.* **83**, 584–594 (2008).
163. Morales, A., Eidinger, D. & Bruce, A. W. Intracavitary Bacillus Calmette-guerin in the treatment of superficial bladder tumors. *J. Urol.* **116**, 180–182 (1976).
164. Alifrangis, C., McGovern, U., Freeman, A., Powles, T. & Linch, M. Molecular and histopathology directed therapy for advanced bladder cancer. *Nat. Rev. Urol.* **16**, 465–483 (2019).
165. Jou, A. & Hess, J. Epidemiology and molecular biology of head and neck cancer. *Oncol. Res. Treat.* **40**, 328–332 (2017).
166. Badoual, C. et al. Prognostic value of tumor-infiltrating CD4+ T-Cell subpopulations in head and neck cancers. *Clin. Cancer Res.* **12**, 465–472 (2006).
167. Badoual, C. et al. PD-1–expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res.* **73**, 128–138 (2013).
168. Welters, M. et al. Intratumoral HPV16-specific T cells constitute a type I-oriented tumor microenvironment to improve survival in HPV16-driven oropharyngeal cancer. *Clin. Cancer Res.* **24**, 634–647 (2018).
169. Fergusson, J. et al. CD161intCD8+ T cells: a novel population of highly functional, memory CD8+ T cells enriched within the gut. *Mucosal Immunol.* **9**, 401 (2016).
170. Gentles, A. J. et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nat. Med.* **21**, nm.3909 (2015).
171. Naik, S. et al. Commensal–dendritic-cell interaction specifies a unique protective skin immune signature. *Nature* **520**, 104 (2015).
172. Rodriguez, R. et al. Memory regulatory T cells reside in human skin. *J. Clin. Invest.* **124**, 1027–1036 (2014).
173. Park, C. & Kupper, T. S. The emerging role of resident memory T cells in protective immunity and inflammatory disease. *Nat. Med.* **21**, 688 (2015).
174. Machado-Santos, J. et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. *Brain* **141**, 2066–2082 (2018).
175. Kuric, E. et al. Demonstration of tissue resident memory CD8 T cells in insulitic lesions in adult patients with recent-onset type 1 diabetes. *Am. J. Pathol.* **187**, 581–588 (2017).
176. Zundler, S. et al. Hobit- and Blimp-1-driven CD4+ tissue-resident memory T cells control chronic intestinal inflammation. *Nat. Immunol.* **20**, 288–300 (2019).
177. Clark, R. A. Resident memory T cells in human health and disease. *Sci. Transl. Med.* **7**, 269rv1–269rv1 (2015).
178. Ho, A. W. & Kupper, T. S. T cells and the skin: from protective immunity to inflammatory skin disorders. *Nat. Rev. Immunol.* **19**, 490–502 (2019).
179. Hawkes, J., Chan, T. & Krueger, J. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J. Allergy Clin. Immunol.* **140**, 645 (2017).
180. Teunissen, M. et al. The IL-17A-producing CD8+ T-cell population in psoriatic lesional skin comprises mucosa-associated invariant T cells and conventional T cells. *J. Invest. Dermatol.* **134**, 2898 (2014).
181. Bhushan, M. et al. Anti-E-selectin is ineffective in the treatment of psoriasis: a randomized trial. *Br. J. Dermatol.* **146**, 824 (2002).
182. Boyman, O., Hefti, H., Conrad, C., Nickoloff, B. & ter, Nestle, F. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-alpha. *J. Exp. Med.* **199**, 731 (2004).
183. Matos, T. R. et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17–producing αβ T cell clones. *J. Clin. Invest*. **127**, 4031–4041 (2017).
184. Cheuk, S. et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. *J. Immunol.* **192**, 3111 (2014).
185. Gilhar, A., Etzioni, A. & Paus, R. Alopecia areata. *N. Engl. J. Med.* **366**, 1515 (2012).
186. Pratt HC, L. E. Jr., Messenger, A. G., Christiano, A. M. & Sundberg, J. P. Alopecia areata. *Nat. Rev. Dis. Prim.* **3**, nrdp201711 (2017).
187. Xing, L. et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat. Med.* **20**, 1043 (2014).
188. Gilhar, A., Ullmann, Y., Berkutzki, T. & Kalish, R. Autoimmune hair loss (alopecia areata) transferred by T lymphocytes to human scalp explants on SCID mice. *J. Clin. Invest.* **101**, 62–67 (1998).
189. Li, J. et al. Laser capture microdissection reveals transcriptional abnormalities in alopecia areata before, during, and after active hair loss. *J. Invest. Dermatol.* **136**, 715 (2016).
190. Ibrahim, O., Bayart, C., Hogan, S., Piliang, M. & Bergfeld, W. Treatment of alopecia areata with tofacitinib. *JAMA Dermatol.* **153**, 600 (2017).
191. de Jong, A. et al. High-throughput T cell receptor sequencing identifies clonally expanded CD8+ T cell populations in alopecia areata. *JCI Insight* **3**, e121949 (2018).
192. Bishnoi, A. & Parsad, D. Clinical and molecular aspects of vitiligo treatments. *Int. J. Mol. Sci.* **19**, 1509 (2018).
193. Richmond, J. M. et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci. Transl. Med.* **10**, eaam7710 (2018).
194. Prosser, A. C., Kallies, A. & Lucas, M. Tissue-resident lymphocytes in solid organ transplantation. *Transplantation* **102**, 378–386 (2018).
195. Turner, D. L., Gordon, C. L. & Farber, D. L. Tissue-resident T cells, in situ immunity and transplantation. *Immunol. Rev.* **258**, 150–166 (2014).