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Perspective

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# Unique properties of tissue-resident memory T cells in the lungs: implications for COVID-19 and other respiratory diseases

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## Abstract

Tissue-resident memory T ($T_{RM}$) cells were originally identified as a tissue-sequestered population of memory T cells that show lifelong persistence in non-lymphoid organs. That definition has slowly evolved with the documentation of $T_{RM}$ cells having variable terms of tissue residency combined with a capacity to return to the wider circulation. Nonetheless, reductionist experiments have identified an archetypical population of $T_{RM}$ cells showing intrinsic permanent residency in a wide range of non-lymphoid organs, with one notable exception: the lungs. Despite the fact that memory T cells generated during a respiratory infection are maintained in the circulation, local $T_{RM}$ cell numbers in the lung decline concomitantly with a decay in T cell-mediated protection. This Perspective describes the mechanisms that underpin long-term T cell lodgement in non-lymphoid tissues and explains why residency is transient for select $T_{RM}$ cell subsets. In doing so, it highlights the unusual nature of memory T cell egress from the lungs and speculates on the broader disease implications of this process, especially during infection with SARS-CoV-2.

## Sections



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## Introduction

Memory T cells can show a range of persistence within non-lymphoid compartments. Many lymphocytes move freely through the various organs unimpeded before exiting the tissue via the draining lymphatic vessels[1–3]. Recognition of antigen leads to their transient retention[4] while physical barriers may slow the return of cells to the circulation[5]. Finally, a subset of T cells is specialized for purely localized patterns of immune surveillance[6,7] and only poorly exits the tissues, if at all[8]. These tissue-resident memory T ($T_{RM}$) cells[9] have a cell-autonomous limitation in their recirculation capacity[10–12] and show a superior ability to control localized infections in a number of settings[13–15]. In this Perspective, I detail the transcription networks that define sequestered $T_{RM}$ cells, identifying $CD103^+CD8^+$ memory T cells as the key population of memory $CD8^+$ T cells that encompasses all the hallmarks of permanent tissue residency. Finally, I describe how these archetypical $T_{RM}$ cells show an unusual pattern of egress from the lungs and discuss how this impacts the course of respiratory infections, including SARS-CoV-2.

## Identifying tissue-resident memory T cells

$T_{RM}$ cells were initially identified as a distinct, sessile T cell subset that coexisted alongside tissue-emigrating T cells[8]. This was a break from the prevailing understanding of tissue T cells based on early lymphocyte circulation experiments[5,16,17]. At that time, the widely accepted view was that these T cells were simply recirculating memory cells that either happened to be found in non-lymphoid tissues in large numbers[18–20] or, alternatively, were trapped by some sort of gating mechanisms or by structural barriers such as the basement membrane that lines epithelia[5]. The identification of a unique $T_{RM}$ cell subset meant that non-lymphoid tissues contained at least two populations of memory T cells, each with its own distinct phenotype and functional properties. One was a recirculating subset that at the time was thought to comprise effector memory T ($T_{EM}$) cells[17] and the other, the newly identified permanently resident $T_{RM}$ cell population.

A major challenge from that point onwards has been distinguishing non-migrating $T_{RM}$ cells from recirculating memory T cells, largely because of the phenotypic overlap between these populations. For example, $T_{RM}$ cells do not express CC-chemokine receptor 7 (CCR7) — a receptor required for entry into lymphoid tissues and the marker that was originally used to differentiate $T_{EM}$ cells (identified as CCR7-negative) from lymphoid-tissue-constrained central memory T ($T_{CM}$) cells (identified as CCR7-positive)[17]. Separately, CD69 had been proposed to be a pan-$T_{RM}$ cell identifier[21], yet it is upregulated by both antigen-specific and nonspecific stimuli[22] and a substantial fraction of migratory T cells express this molecule once in the tissues[23]. Compounding the confusion is the extensive heterogeneity seen in both circulating and tissue-resident memory T cell populations[24–27], expanded by a history of natural infection[28]. Therefore, although combinations of surface markers can cover a range of $T_{RM}$-like tissue cells, it would be fair to say that to date there remains no unifying phenotypic identifier for this population.

## $CD103^+CD8^+$ $T_{RM}$ cells: the archetypical $T_{RM}$ cell

Although it has proven difficult to identify $T_{RM}$ cells by definitive phenotypic means, therapeutic and experimental interventions can eliminate all circulating T cells from the blood, leaving long-term tissue residents as the only memory T cells remaining in non-lymphoid compartments. Two approaches have proven particularly useful in this regard. The first exploits T cell responses against a transplantation mismatch to selectively eliminate cells in the circulation[29–31] whereas the second uses a more versatile cytolytic antibody-based technique for the same purpose[27,32,33]. Of additional importance is the in vivo infusion of labelling antibodies before tissue analyses to exclude cells that are simply in the vasculature[34]. This technique eliminates confounding contributions by blood-borne cells and is critical when examining highly vascularized organs such as the lung, although it does not identify $T_{RM}$ cells per se.

One of the striking features of the mouse $T_{RM}$ cells that remain after circulating T cells are depleted from the tissues is the dominance of a population of $CD8^+$ T cells expressing the CD103 (also known as αE integrin) subunit of the αEβ7 integrin complex[23,33]. $CD103^+$ $T_{RM}$ cells are highly enriched in the environmentally exposed epithelia of the skin, small intestine and female reproductive tract[8,10,35]. At these epithelial sites, interaction between αEβ7 and its abundantly expressed target ligand E-cadherin[36] probably plays a role in cell adhesion and retention. However, $CD103^+CD8^+$ $T_{RM}$ cells are also found in non-epithelial tissues such as the brain[12,37], and although CD103 has variously been implicated as being important for $T_{RM}$ cell development[38–40], its expression is not ubiquitous[37] and therefore not mandatory for all forms of T cell residency. Nonetheless, tissue-lodged $CD103^+CD8^+$ memory T cells are highly resistant to equilibration across parabiotic pairs[41], are uniquely spared from elimination by the approaches mentioned above[23,30], selectively survive for prolonged periods in transplanted tissues in mice[8,33] as well as in humans[42,43] and persist independently of antigen recognition[15,37]. Moreover, $CD103^+CD8^+$ memory T cells are usually not found in secondary lymphoid organs[15,44] — with one striking exception[45,46] to be described in detail below. Thus, although not all $T_{RM}$ cells express CD103, the balance of evidence argues that $CD103^+CD8^+$ tissue T cells are true $T_{RM}$ cells, making this an easily identifiable archetypical population and an ideal reductionist means for delineating tissue residency mechanisms.

## RUNX3 and TGFβ in $CD8^+$ $T_{RM}$ cell development

Early experiments in mice comparing the transcriptomes of $CD103^+CD8^+$ $T_{RM}$ cells isolated from a range of organs with those of their circulating counterparts provided some of the first insights into the transcription networks critical for $T_{RM}$ cell development and survival[10,39]. Not surprisingly, genes associated with tissue egress were found to be downregulated in $T_{RM}$ cells, including *Ccr7* and the genes encoding the sphingosine-1-phosphate receptors S1PR1 and S1PR5[10,11]. Without the downregulation of these receptors, the precursors of $T_{RM}$ cells return to the circulation, thereby dampening $T_{RM}$ cell development[11,47]. Other genes that come into play are those involved in dealing with local metabolite availability[7,48,49] and those that prolong T cell survival[23], with both sets of genes necessary to maintain a long-lived sequestered T cell population. Further experiments fleshed out how transcription factors control the various networks, such as the involvement of KLF2, which modulates the expression of S1PR1 and CCR7[11]. Following this, key upstream gene regulators were identified, such as T-bet and EOMES[23,50] as well as BLIMP1 and the BLIMP1 homologue HOBIT[51,52]; of note, BLIMP1 and HOBIT are also involved in the development of innate-like lymphocytes that permanently reside in mouse tissues, such as natural killer cells and natural killer T cells[51]. Most recently, an overarching transcription factor has come into focus. RUNX3 has been identified as contributing to $T_{RM}$ cell formation, and it directly or indirectly regulates BLIMP1 and KLF2 expression as well as modulating downstream retention components[53]. This contribution is particularly striking as RUNX3 is a pivotal player in $CD8^+$ T cell development and functionality[54,55].

As the network analyses evolved, one commonality to emerge was the involvement of TGFβ in $T_{RM}$ cell development and survival

in a range of tissues and organs[23,40,56–58]. TGFβ appears to use a non-canonical signalling pathway[59] that controls much of the CD8$^+$ $T_{RM}$ cell gene expression signature[60]. It has been shown to facilitate tissue entry via selectin upregulation[61] and can regulate a broad range of transcription regulators and cytokine-driven survival factors during CD8$^+$ $T_{RM}$ cell development[11,23,50]. Combined, there is now a wealth of data regarding the tenets of transcriptional control of $T_{RM}$ cell formation, which largely pivots around a TGFβ–RUNX3 axis, at least in the case of the mouse CD8$^+$ $T_{RM}$ cell subset.

## $T_{RM}$ cell re-entry into the circulation

Although $T_{RM}$ cells were originally shown to persist in non-lymphoid organs in quasi-perpetuity[8], there have been subsequent descriptions of $T_{RM}$ cell egress with the resultant 'ex-$T_{RM}$ cells' ultimately being incorporated into the circulation[33,41,62]. CD8$^+$ $T_{RM}$ cell numbers show an intrinsic decline in organs such as the lung and liver[30,41], but not in tissues such as the skin and small intestine, where the cells effectively remain in place for life once lodged[8,41]. However even for these fixed populations, $T_{RM}$ cells can be forced to leave using in situ antigen stimulation via peptide challenge[33,44]. Such active dislodgement is not universal, with CD103$^+$CD8$^+$ $T_{RM}$ cells sometimes remaining resident in the tissue even after multiple rounds of cell division initiated by local infection[8,63,64]. Perhaps tellingly, when CD103$^+$CD8$^+$ $T_{RM}$ cells are selectively dislodged by intervention, the resultant ex-$T_{RM}$ cells appear to adopt a phenotype intermediate between those of upstream resident memory T cells and conventional recirculating memory T cell populations, with a CD103 expression status that is either undefined or reported to be transient[33,44]. Moreover, when these same cells are directly isolated from non-lymphoid compartments, they are inferior in their capacity to enter the circulation compared to counterparts extracted from lymphoid organs[33,65].

It remains difficult to reconcile these conflicting results, but studies on CD8$^+$ $T_{RM}$ cells in the liver and recent revelations regarding the basis for CD4$^+$ T cell residency provide valuable insight that might explain egress variability. Although much more is known about CD8$^+$ $T_{RM}$ cells, there are many examples of CD4$^+$ $T_{RM}$ cell-type counterparts[13,27,66]. Comparisons make it clear that the two are unrelated in terms of mechanistic underpinnings and they can exhibit quite distinct patterns of tissue residency even in the same organ[29,67]. As noted above, the archetypical CD103$^+$CD8$^+$ $T_{RM}$ cells use a set of TGFβ-driven transcriptional networks to shut down tissue egress, upregulate survival factors and tailor metabolic pathways. By contrast, few of these networks have been associated with CD4$^+$ $T_{RM}$ cell residency, which instead relies on retention mechanisms variously operating via cell aggregation, antigen-specific T cell activation and chemotactic agents[68,69] (Fig. 1). The reason why CD4$^+$ and CD8$^+$ $T_{RM}$ cells are likely to differ at the mechanistic level is the pivotal role RUNX3 plays in $T_{RM}$ cell development and survival[53]. This transcription factor is repressed in CD4$^+$ T cells by the opposing gene regulator ThPOK (also known as ZBT7B), which is itself a lineage-determining factor[70,71]. Although natural RUNX3 upregulation can convert CD4$^+$ T cells to an unconventional CD8αα$^+$ intraepithelial regulatory T cell population with CD8$^+$ $T_{RM}$ cell-like qualities[72], the intrinsic paucity of RUNX3 expression in conventional CD4$^+$ $T_{RM}$ cells results in low CD103 levels in these cells and more transient tissue residency as a direct consequence of their inability to access the RUNX3-mediated pathways downstream of TGFβ signalling[53,73].

Somewhat analogous to their CD4$^+$ tissue-resident T cell counterparts, mouse liver CD8$^+$ $T_{RM}$ cells are also deficient in CD103 expression[74]. These cells show medium-to-long-term tissue residency[74], but not the almost lifelong persistence of $T_{RM}$ cells in organs such as skin and small intestine[41,65]. Although the liver T cells are fully capable of responding to TGFβ, local requirements negate this capacity, resulting in an immature or less differentiated CD103$^-$ $T_{RM}$ cell population (Fig. 1) with an inferior term of residency combined with more flexible reprograming compared to mature CD103$^+$ $T_{RM}$ cell counterparts[65]. Collectively, the results show that although CD103$^-$ $T_{RM}$ cells can reside in tissues for a considerable period, they can exhibit a range of spontaneous egress and reprogramming capabilities because of deficiencies in TGFβ-mediated maturation. Given the heterogeneous nature of tissue-resident T cells, including variable CD103$^+$ T cell content across different organs[37] and the known recruitment of recirculating T cells by the peptide stimulation used for $T_{RM}$ cell dislodgement[32], it is possible that less differentiated populations analogous to the liver CD103$^-$ $T_{RM}$ cells may preferentially contribute to the egress process. Regardless, although some $T_{RM}$ cells can leave the tissues and enter the circulation, the balance of data argues that for the archetypical CD103$^+$CD8$^+$ $T_{RM}$ cells, this process is not constitutive and when it does happen, it usually results in cells that do not phenocopy their direct upstream antecedents.

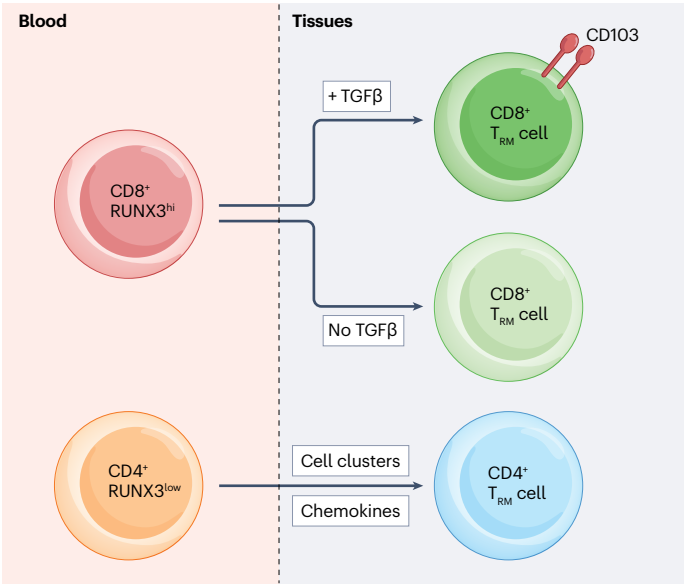


**Fig. 1 | Subtypes of tissue-resident memory T cells based on transcription profiles.** The mechanism promoting permanent residency in non-lymphoid tissues for the CD103$^+$CD8$^+$ tissue-resident memory T ($T_{RM}$) cell population involves a RUNX3-driven transcriptional network that is downstream of TGFβ receptor signalling[53,60]. This transcription programme is missing in CD4$^+$ $T_{RM}$ cells as a consequence of deficiencies in RUNX3 expression[73]. Instead, these populations use a combination of cell aggregation and extrinsic chemokine networks for tissue retention[68,69]. The typical CD103$^+$CD8$^+$ $T_{RM}$ cell transcription programme is also missing in CD103$^-$ liver-like $T_{RM}$ cells because of deficiencies in TGFβ engagement[65].

## $T_{RM}$ cells in the lungs

From the discussion above, it can be reasonably argued that because they fully engage the TGFβ–RUNX3 residency programme, mouse CD103$^+$CD8$^+$ tissue T cells fit the original $T_{RM}$ cell definition[8]; specifically,

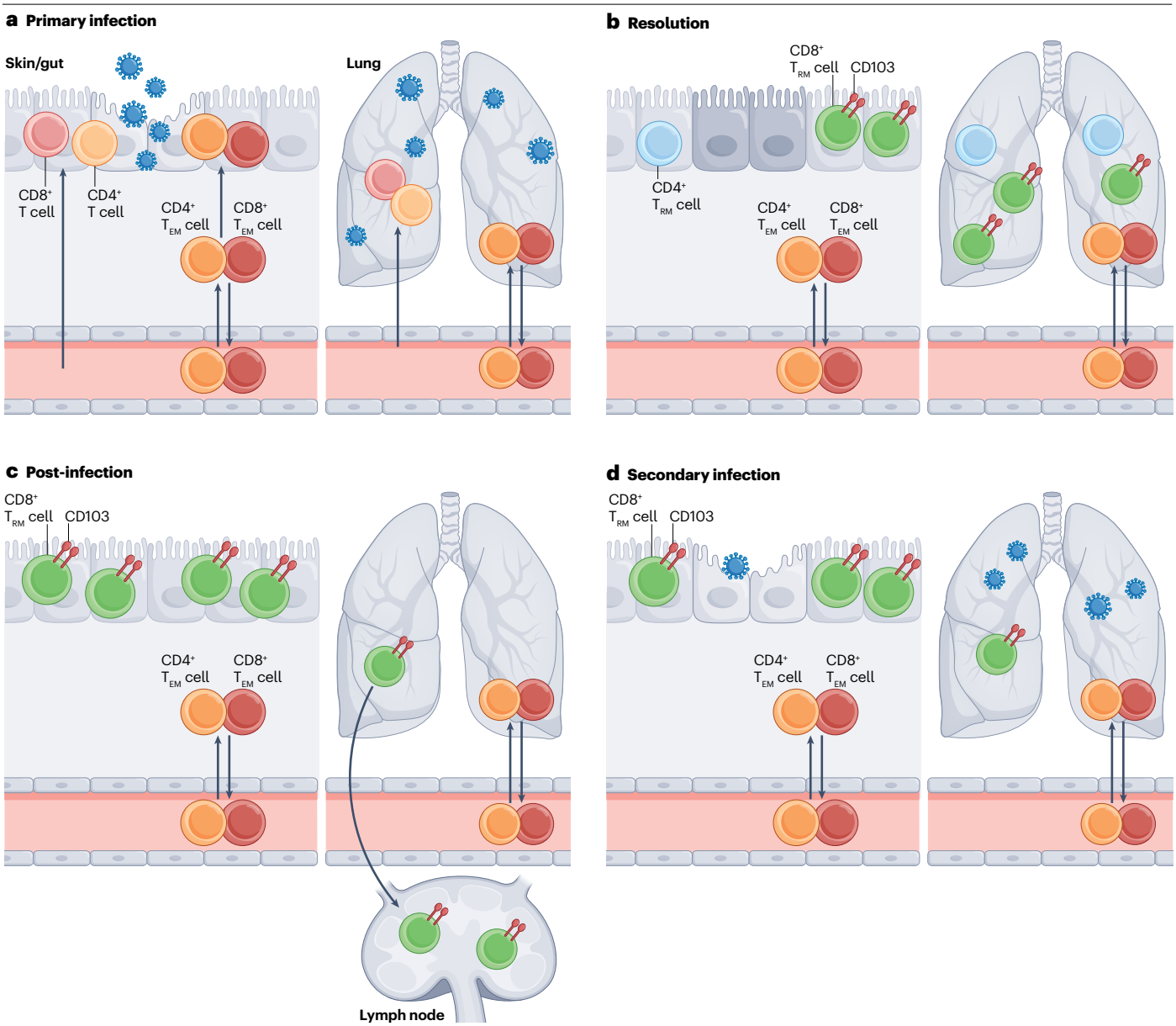


**Fig. 2 | Selective and constitutive egress of lung CD103$^+$CD8$^+$ $T_{RM}$ cells.** Inflammation associated with infection of tissues such as skin, small intestine and reproductive tract (left panels) and lung (right panels) leads to the recruitment of a variety of CD4$^+$ and CD8$^+$ T cells that combat the invading pathogens (part **a**). These populations include effector memory T ($T_{EM}$) cells that continuously recirculate between non-lymphoid organs and blood as well as tissue-resident memory T ($T_{RM}$) cell precursors (not shown). Following resolution of the infection (part **b**), most of the recruited T cells exit or die, leaving local immunosurveillance to recirculating $T_{EM}$ cells and the more potent $T_{RM}$ cells. Over time, some $T_{RM}$ cell subsets selectively disappear (part **c**, left panel), resulting in a resident population highly enriched in long-lived CD103$^+$CD8$^+$ $T_{RM}$ cells that afford long-term local immunity against re-infection (part **d**, left panel). In the lungs, CD103$^+$CD8$^+$ $T_{RM}$ cells are gradually lost after the infection has resolved and instead accumulate in the proximal draining lymph nodes (part **c**, right panel) leaving the lower respiratory tract deficient in CD103$^+$CD8$^+$ $T_{RM}$ cells and thus susceptible to re-infection (part **d**, right panel).

they form a distinct subset of memory T cells that remains lodged in peripheral compartments in virtual perpetuity. However, there is one organ where the CD103$^+$CD8$^+$ T cells do not abide by this rule, and its uniqueness has important disease implications. Unlike the situation in other tissues, CD103$^+$CD8$^+$ $T_{RM}$ cells in the lung do not require local antigen stimulation for dislodgement[45]. Also unusually, the egressing memory T cells retain cell surface expression of CD103 post-exit, meaning that the lung-draining lymph nodes are unique in having a substantive subset of memory CD8$^+$ T cells with this marker[45,46]. Lung CD103$^+$CD8$^+$ $T_{RM}$ cells are fully mature and unremarkable in terms of their TGFβ requirement for development and survival[58]. They also express the gene signatures associated with tissue residency[10,12],

including a cluster of $T_{RM}$ cell-associated transcription factors, namely HOBIT, NR4A1, aryl hydrocarbon receptor (AhR) and BHLHE40[7,51,75,76]. In all critical aspects, they resemble $T_{RM}$ cells from other tissues, meaning that their exit from the lung is probably an organ-specific feature rather than due to a cell-intrinsic programme. Such a mechanistic distinction is important, as it would suggest that the egress process would probably capture $T_{RM}$ cells beyond the archetypical $CD103^+CD8^+$ subset that was used to define this phenomenon and would do so regardless of where they fall on a maturation and term-of-residency continuum.

Exacting experiments by Stolley and colleagues[45] proved that the resultant draining lymph node-resident memory T cells were indeed constitutively derived from upstream lung tissue counterparts, possibly dislodged as a consequence of virus-induced tissue damage[77,78] or the interruption of tonic TGFβ signalling needed to retain $T_{RM}$ cells in tissues[79]. Although the resultant lymph node accumulation offers an additional avenue to maintain regional protection[45,80], memory T cell exit helps to explain one of the intriguing conundrums associated with immune protection in the lungs. It has long been known that T cell immunity in the lung wanes over time, with this first reported for respiratory infections with influenza virus and Sendai virus in mice[81,82]. This decline in lung-based immunity occurs despite virus-specific memory cells persisting in the circulation[30,82–84]. Non-$T_{RM}$ cell-based mechanisms were originally proposed to describe the behaviour of lung T cell populations[81,85–87], variously confounded by blood-borne cells that are particularly problematic when dealing with this highly vascularized organ[34]. More recently, it was shown that the waning local immunity correlates with declining lung $T_{RM}$ cell numbers in mouse after influenza virus infection[83,84] and in humans after respiratory syncytial virus challenge[88]. Although other mechanisms have been posited to account for this $T_{RM}$ cell attrition, such as the selective death of lung $T_{RM}$ cells[30,84] or the disappearance of structures associated with focal damage[67], none exclude concurrent tissue egress. Once lost, lung $T_{RM}$ cells are difficult to replace in the absence of renewed infection owing to the strict antigen recognition requirements for effective lodgement[67,83,89], which are optional in many other tissues[37] including the upper respiratory tract[90]. Overall, a range of mechanistic overlays would imply that losing $T_{RM}$ cells over time is important for this organ — for example, to limit ongoing damage to its delicate oxygen-exchange architecture[91].

Finally, the natural decay of lung $T_{RM}$ cells stands in stark contrast to what is seen elsewhere in the body, where $CD103^+CD8^+$ $T_{RM}$ cell populations can remain tightly contained (Fig. 2). $CD103^+CD8^+$ $T_{RM}$ cells show long-term persistence in organs such as the brain, skin and cervicovaginal tissue[8,39,92], despite the loss of their $CD103^-$ counterparts. The extent to which these spatial and temporal restrictions can operate was dramatically illustrated by experiments that lodged $CD103^+CD8^+$ $T_{RM}$ cells in a small patch of skin, thus confining effective protection to just that location while leaving the remainder of the torso under the inferior control of memory cells in the blood[8,63]. By contrast, lung $T_{RM}$ cell residency is unstable and transient, resulting in surveillance that is increasingly dependent on recirculating populations over time, with a concomitant decline in local T cell immunity.

## $T_{RM}$ cell lung egress and immunity to SARS-CoV-2

At the time of this writing and nearly three years since the emergence of the SARS-CoV-2 virus in late 2019[93,94], the COVID-19 pandemic continues to be a major challenge in many parts of the world. Despite reports showing that circulating antiviral T cell immunity can be cross-reactive against emerging variants[95], long lived[96,97] and associated with better disease outcomes[98,99], immunity from combinations of COVID-19 vaccination and SARS-CoV-2 infection has been found to steadily decline[100,101]. One possible contributor may be that anti-SARS-CoV-2 tissue-resident T cells that are pivotal for immune protection show the same type of numerical decay as reported for mouse $CD103^+CD8^+$ $T_{RM}$ cells. Employing strategies that slow $T_{RM}$ cell loss[102] could be advantageous, as might approaches that circumvent the lung altogether. The upper respiratory tract, especially the nasal mucosa, is a prime target with respect to the latter possibility as it does not show the $T_{RM}$ cell decline that is intrinsic to the lung[90]. Alternatively, it may be that $T_{RM}$ cells are actually counterproductive, leading to tissue damage. This is especially poignant because repeated antigen encounters extend the durability of $CD103^+CD8^+$ $T_{RM}$ cells in the lung[102], yet a recent report found that experiencing successive SARS-CoV-2 infections progressively increases the risk of adverse health outcomes[103]. In terms of their potential to contribute to tissue damage, TRM cells have an innate immune alarm and recruitment function[32,104], and the innate response has been shown to be a key mediator of COVID-19-associated lung pathology[105,106].

## Conclusion

Overall, $T_{RM}$ cells provide superior protection against tissue-localized infection, primarily because of constraints in their migration capabilities. Despite proving to be long-lived and effective in a range of different infectious diseases, lung $T_{RM}$ cells have an unusual propensity for tissue exit reflected in a decay in local T cell immunity. Such a feature may have evolved to protect this organ against long-term damage or may simply be a by-product of some unique anatomical feature intrinsic to lung function. Given the ability of $T_{RM}$ cells to respond to infection with an immediacy unmatched by the blood-based memory populations, there is a need to focus on their deposition in the different compartments of the respiratory system, especially in settings or sub-regions that support their long-term survival.

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