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Parallel worlds of the adaptive and innate immune cell networks

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Adaptive and innate immune cells have typically been functionally and temporally segregated even though they share a number of salient features. Over the past decade, significant advances have been made in understanding the composition and diversity of both innate and adaptive cell populations. This has shed light on how cells from two distinct pathways are so highly complementary. Innate lymphoid cells (ILCs) are pivotally positioned in tissues to form a stable population akin to tissue-resident T cells that protects the body. Nevertheless, the pathway by which different lymphocytes enter tissues, terminally differentiate and are replenished to maintain populations remains incompletely understood. Recent evidence challenges our assumptions about the sedentary lifestyles of so called 'tissue-resident cells' and pushes us to consider their roles in orchestrating protection of the immune system beyond the classical models.

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Introduction

Immune cells are largely concentrated in primary and secondary lymphoid tissues, but it is increasingly clear that a vast number of lymphocytes can accumulate in non-lymphoid tissues even at steady-state. These cells affect critical functions in maintaining immune homeostasis together with mediation of responses to infectious or inflammatory stimuli.

'Tissue residency' refers to immune cells that establish in the tissue parenchyma or stroma where they can reside for an extended period of time without moving from tissue to tissue. Demarcating immune cells into 'tissue-resident' versus 'circulating' cells provides a framework for defining two patterns of immune cell behavior matching the specialized functions of these cells. Circulating cells move between the blood and secondary lymphoid tissues, while tissue-resident immune cells move between the blood and nonlymphoid tissues thereby establishing long-term within the peripheral compartments. Tissue-residency implies that cells are relatively fixed or static in tissues providing a mechanism by which immune surveillance can be effectively executed through sampling of constituents of the blood or lymph that filter through organs. This makes them potent controllers of infection at the point of entry of infectious organisms to the body and provides a time and energy efficient method of eliminating pathogens.

The classic paradigm in immunology involves innate immune cells residing at barriers and in tissues mediating front-line defense, while adaptive cells undergo a series of triggers to arm them with effector molecules and migratory potential to continuously patrol for pathogen invaders and recruit the larger secondary army. This was challenged when it was discovered that some T cells remained in non-lymphoid tissues for much longer than anticipated [1,2] and this retention was governed by specific interactions between lymphocyte receptors and the extracellular matrix [3]. These initial studies ushered a number of elegant studies [4–7] that demonstrated that T_{RM} are both located, and functionally different from, effector and memory cells allowing $CD8^+$ T cells to establish their weaponry alongside innate cells at the frontier of tissue invasion.

The concept of tissue-residency initially emerged from studies of a distinct subset of $CD8^+$ memory T cells which develop within the affected tissues following a primary infection or insult and do not spread beyond this point or contribute to the circulating pool [4]. Now, it has become increasingly clear that other immune cell types exhibit tissue-residency and establish relatively stable populations within non-lymphoid tissues. For example, tissue-resident regulatory T cells (Tregs) have been defined and these cells exhibit a different transcriptome from other non-lymphoid tissue Treg populations and accumulate as animals age [8]. Deeper investigation revealed that this population of Tregs undergo an unexpected multi-step maturation program that relies on priming in the spleen before exiting the lymphoid tissue and establishing in non-lymphoid tissues accompanied by a final

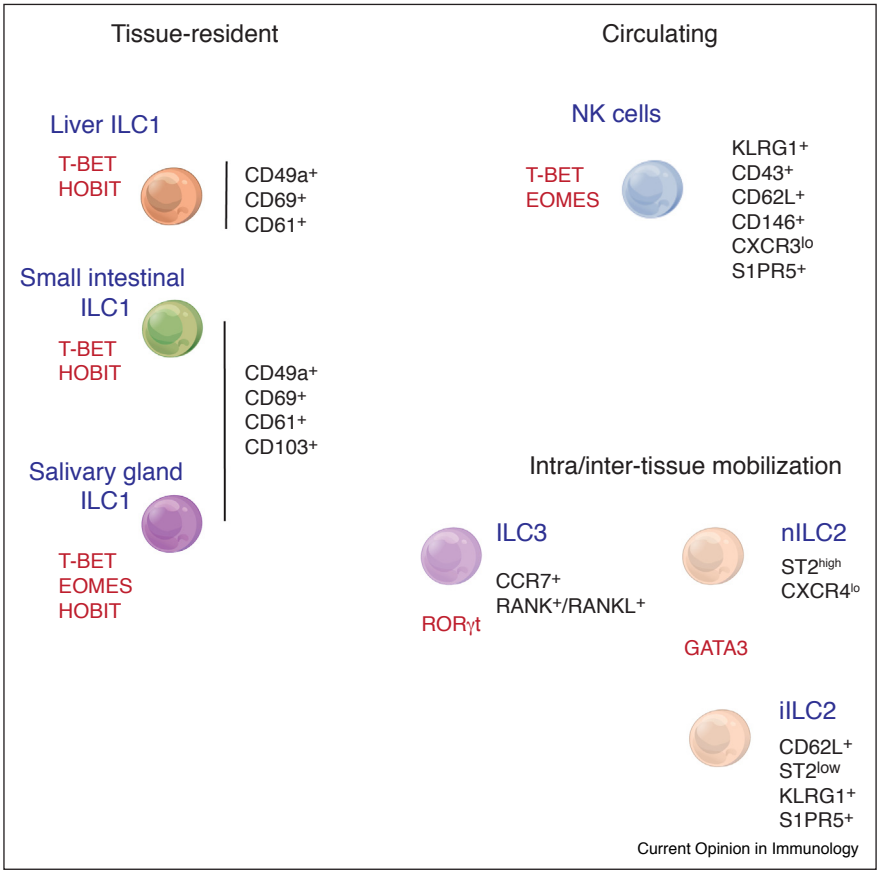
diversification in the visceral adipose tissue [9•] (Figure 2). Collectively, these studies highlight the complexity of the lifecycle of lymphocyte lineages as they establish tissue residency.

In the innate system, ILCs have been seen as long-term inhabitants statically embedded in peripheral tissues and largely lacking a pathway for circulation around the body. The level of tissue residency has mainly been determined using parabiosis. In this approach, the vasculature of two mice is conjoined allowing circulating lymphocytes to exchange between the two hosts. Strikingly, T_{RM} and ILC fail to exchange at a very low frequency within the reference timeframe of the experiment leading to the notion that this is not their typical pathway [10–12,13•]. After initial seeding, expansion and maturation of ILCs, little redistribution of these cells was found to occur at steady-state. Under inflammatory conditions ILCs greatly expanded, but their relocalization to different tissues remained modest [13•,14]. While the data strongly support the static nature of these populations, it does not discount the possibility that the maintenance of tissue-resident cells may depend on circulating progenitors which are not generated *in situ*, nor that circulating cells adopt a phenotype distinct from the mature tissue-resident cells obscuring their detection, like ILC progenitors in humans [15•]. Detailed genomic profiling has revealed that tissue-resident cells differ both transcriptionally and metabolically from their circulating counterparts [16,17•,18] and these alterations are likely to markedly skew our modeling of the circulatory and migratory pathways undertaken by ILCs.

Factors required to establish residency of T_{RM}

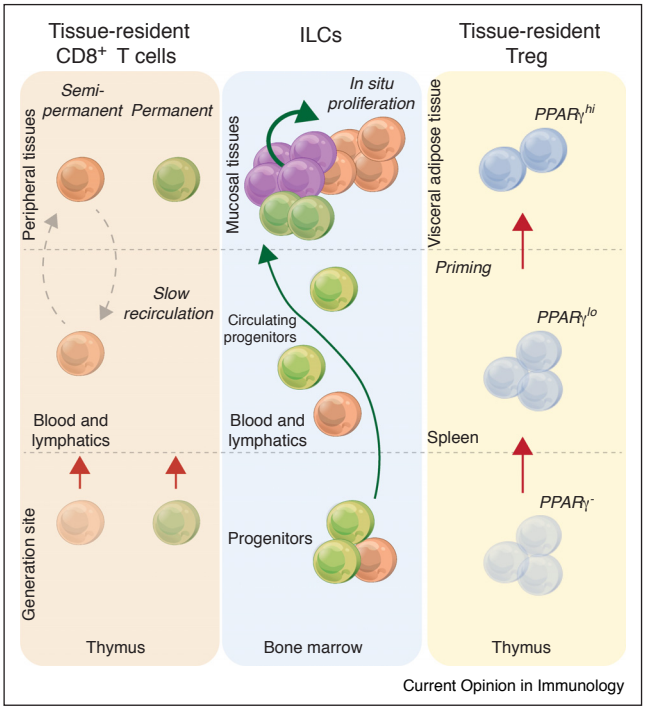
The hallmarks of tissue residency are defined by (i) core surface receptors which include CD69, CD103, CD49a and CD44, (ii) homing molecules such as S1PR and (iii) metabolic activity (Figure 1). Critically, CD103 and CD49a (VLA-1, very late antigen-1) not only define key markers of T_{RM} but form the binding partners for the ligands E-cadherin and collagen, respectively, that tether cells within the tissues [3]. CD44, like CD103 and CD49a, is a receptor for hyaluronic acid, a component of the extracellular matrix [19,20]. Classically, CD44 is a marker of T cell activation on newly generated effector cells but functionally it is also likely to be important in T_{RM} [21,22].

Figure 1



Surface receptors (black) and transcription factors (red) that promote resident or migratory behavior of different ILC subsets in mice between or within tissues.

Figure 2



Tissue-residency defines the final dominant destination of an immune cell. The pathway to tissue-residency is typified by three different scenarios. Firstly, following activation, tissue-resident CD8$^+$ T cells localize to peripheral tissues and largely remain at that site while a smaller fraction of cells are retained for long periods but can slowly recirculate. In the second setting, ILCs localize in mucosal tissues and do not undergo recirculation but largely replenish through slow division at the tissue site. However, progenitors that exhibit a phenotype distinct from mature cells, are likely to travel in the circulation for deposition in non-lymphoid tissues, particularly mucosal sites. The third pathway highlights the importance of intermediary tissues such as the spleen where Tregs destined to become visceral adipose tissue-resident cells undergo a priming phase which is an essential part of their developmental pathway. Expression of PPARγ is also upregulated to facilitate the cellular metabolism requirements in adipose tissue.

Transcriptional regulators of T_{RM}

Governance of the T_{RM} phenotype is orchestrated via a constellation of transcription factors. These include HOBIT (homolog of Blimp1 in T cells or ZNF683), BLIMP1, KLF2, RUNX3, T-BET and EOMES. In mice, HOBIT and BLIMP1 cooperate synergistically to regulate the expression of genes involved in retention of cells in tissues, and their egress [18]. This is largely mediated by their regulation of two T-box transcription factors T-BET and EOMES which when downregulated induce responsiveness to TGF-β and upregulation of CD103 [23,24]. Low levels of T-BET are, however, essential to maintain responsiveness to IL-15 enabling the formation of T_{RM} and their function [25]. The HOBIT-BLIMP1 transcriptional module is also required to regulate other tissue-resident lymphocytes such as natural killer T (NKT) cells and liver-resident ILC1 [18] (Figure 1). Interestingly, the role of HOBIT in ILC1 is not consistent between ILC1s from different organs. HOBIT is expressed by ILC1s across organs such as the salivary gland and small intestine and yet only liver ILC1s are affected by the loss of HOBIT [26]. Many factors may be involved in regulating the egress of cells from a tissue and it cannot be assumed that transcription factors associated with tissue residency will have conserved functions in all organs. In human tissues, HOBIT is more broadly expressed than in mouse tissues while T_{RM} also lack expression of T-BET and EOMES. Thus, how HOBIT fits into the picture as a key regulator not completely clear. HOBIT expression in man occurs at lower levels on both circulating and tissue resident CD8$^+$ T cells but is strongly expressed in natural killer (NK) cells suggesting that its role in defining T_{RM} is not universal across species [27]. T_{RM} cells in humans appear to depend more closely on factors such as NOTCH-1 and HIF-1α, or organ-specific factors such as RUNX3, BATF (Basic Leucine Zipper *ATF*-Like Transcription Factor), AHR (aryl hydrocarbon receptor) and AP-1 as seen in the lung [28]. RUNX3 has been shown to regulate circulating effector T cells but also directs the differentiation and maintenance of CD103$^+$ T_{RM} cells [29•]. Both NOTCH-1 and AHR are necessary for the maintenance of T_{RM} cells [17•,28,30]. Collectively, multiple transcription factors have a significant impact on the development of T_{RM}, and true master regulators have not yet been fully established. Nevertheless, a distinct set of genes, overlaid by local tissue influences, may universally define these cells (Figure 1).

T_{RM} also appears to have important roles in tumors, particularly those lodged in peripheral tissues. This is well illustrated by several recent studies that demonstrate a positive association between T_{RM} cells and an enhanced clinical outcome for melanoma, breast tumors, lung adenocarcinoma, ovarian carcinoma and the efficacy of cancer vaccination [7,31–36]. Tumor-infiltrating T cells are a heterogeneous population that include effector, effector memory and T_{RM}. Single cell RNA sequencing of infiltrating CD8$^+$ T cell within tumors identified T_{RM} gene signatures that could be clustered based on their level of expression of previously characterized immune checkpoints genes including PD-1, TIM-3, CTLA-4, LAG3 and TIGIT, or mitotic genes [34,35]. In breast cancer, the T_{RM} gene signature was associated with a significantly better prognosis in early stage triple-negative breast cancer, a subtype of breast cancer with an aggressive clinical behavior [35]. The efficacy of anti-PD-1 treatments observed in patients harboring triple-negative tumors [37] suggest that they may rely on PD-1^{high}-expressing T_{RM} cells much more than CD8$^+$ non-T_{RM} (CD8$^+$CD103$^-$) cells as the clinical prognosis was aligned to a significantly enriched baseline T_{RM} gene signature in responders to anti-PD-1 therapy [35]. In lung

adenocarcinoma, three clusters T_{RM} were identified [34]. Strikingly, one cluster expressed many more immune check-point genes than the other two clusters. Interestingly, patients that showed poorer enrichment for T_{RM} genes that included immune check point genes had improved survival outcomes [34]. These studies illustrate the complexity and heterogeneity of tumor-infiltrating T cells even within the T_{RM} subset which has thought to be a relatively homogeneous population. Collectively, these results highlight the central importance of having high quality, rather than a large number of, infiltrating T cells to influence patient survival.

Tethering and letting go

While transcription factors are essential in dictating the developmental pathway of T_{RM}, retention in tissues depends on mechanisms that tightly regulate lymphocyte tethering and egress to ensure stable positioning within tissues and at barrier surfaces for front-line immune protection. The most well studied receptor ligand pairs that establish tethering are CD103 and E-cadherin, and CD49a and collagen [3,16,17•]. Loss of either of these receptor/ligand partners via blocking or genetic deletion results in continuous circulation of cells in the blood without establishment in the tissues. Transforming growth factor (TGF)-β induces CD103 expression and promotes retention of both $CD8^+$ memory T cells and salivary gland ILC1, but not liver or gut, ILC1 [17•,23,38,39]. The capacity to 'leave' tissues is dictated by receptors such those in the S1PR family. S1PR1 mediates chemotaxis of T cells toward sphingosine-1-phosphate found in lymphatic endothelial cells and efferent lymph [40]. S1PR1 is antagonized by CD69 which assists in maintaining T_{RM} in the skin epidermis and lungs [17•,41]. It is regulated by multiple transcription factors including HOBIT/BLIMP1, KLF2 and RUNX3 [18,28,29•,42,43].

Similar to T_{RM}, ILC appear to be almost exclusively tissue-resident at steady-state. Under parabiotic conditions exchange between conjoined mice is negligible even two months after surgery. This is in stark contrast to T cells which show ~50% interchange between the respective hosts [13•,44•]. Despite this, ILC exhibit an array of chemokine and cytokine receptors that suggest they have the capacity to become mobile and may not be permanently resident. NK cells express S1PR5, which is regulated by T-BET, and is critical for the egress of NK cells from the bone marrow and lymph nodes [45–47]. L-selectin, or CD62 ligand (CD62L), is expressed by most lymphocytes including naïve and memory $CD8^+$ T cells but on activation is cleaved as on effector T cells which allows them to enter the circulation and migrate to non-lymphoid tissues and sites of inflammation. Similarly, the ability of NK cells to return to lymphoid tissues is dependent on CD62L expression. A subset of activated or inflammatory $KLRG1^+ST2$ (IL-33 receptor)^{low} ILC2, are highly responsive to stimulation with IL-25 or helminth-induced activation and can develop into circulating cells [44•]. These cells express the receptor S1PR5 similar to NK cells and exhibit S1P-mediated chemotaxis enabling mobilization into the circulation and deposition in distant tissue sites [45]. The failure to detect migration in ILC2 previously might be attributable to the use of antibiotics that potentially downregulate the ability of microbes to induce homing receptors [13•]. ILC2 can also be mobilized from bone marrow in response to a fungal aeroallergen challenge with *Alternaria* extract through ST2-dependent downmodulation of CXCR4 [48] while chronic allergen exposure promotes an increase in blood and lung ILC2 through a β2 integrin-dependent manner [49]. Using the elegant Kaede transgenic mouse in which photoconversion of fluorescent dyes can be induced to tag individual ILC, $ROR\gamma t^+$ ILC3 were shown to migrate from mucosal and peripheral sites to local secondary tissues. For LTi-like ILC3 at least, this depended on CCR7 expression [50] while positioning of ILC3 in cryptopatches relies on RANK/RANKL-mediated signals [51]. Thus, stability of ILC in tissues is likely to be important to their protective functions at steady-state while tissue-specific and systemic inflammatory cues drive multiple signals to mobilize ILC populations to effector sites paralleling the induction of adaptive immune cells (Figure 2).

Functional changes in tissue residency

The metabolic state of immune cells is essential for their survival and to repopulate distinct tissue sites. These metabolic constraints on glucose and oxygen availability are reflected in the adaptations of lymphocytes in different tissue microenvironments. Effector and effector memory T cells rely on aerobic glycolysis to catabolize glucose but T_{RM} are positioned within the parenchyma of tissues such as the lung, epidermis or solid tumors that are typically low in glucose and require different energy programs. P2RX7, a receptor for adenosine triphosphate (ATP), is vital for the generation and maintenance of memory cells, specifically memory precursor and central memory T cells which exhibit higher energy requirements compared with effector and effector memory T cells. Long-lasting memory cells express higher levels of P2RX7 to sense extracellular ATP, a signal released by damaged cells. In preparation for the increase in energy requirement, metabolic reprogramming occurs, whereby the mitochondria is modified for more efficient oxidative phosphorylation. T_{RM} also have high expression and dependency on the P2RX7 receptor for their development and maintenance [52•]. It is not known whether P2RX7 regulates their metabolism, but it is likely that maintenance of long-lived memory and T_{RM} will have similar metabolic requirements and regulatory mechanisms.

In the skin, T_{RM} preferentially use the free fatty acid transporters FABP4 and FABP5 to metabolize fatty acids. These transporters are also required for the survival of

T_{RM} in both normal and psoriatic skin and lung [53•]. Fatty acids are a substrate found in the skin, lung, the gut through the action of bacteria [54] and are abundant in melanomas. They are important contributors to energy generation but also enhance molecules such as acetyl-CoA which drive the production of cytokines such as IFN-γ [55]. However, conditions in different tissues vary both anatomically and temporally as in the case of increasingly hypoxic conditions that might emerge in the setting of tumors as they grow in size. This alters the oxygen concentration which is essential for fatty acid catabolism. Thus, it is likely that tissue-resident immune cells have specific but multiple strategies for coping with the dynamic environment in which they reside (Figure 2). Peroxisome proliferator-activated receptor γ (PPARγ), also known as NR1C3 (nuclear receptor subfamily 1, group C, member 3) regulates glucose metabolism and is expressed by a variety of immune cells including ILC2, NKT cells and Treg cells. Treg cell expansion in adipose tissue is directly induced by IL-33 [56] and ILC2 express both PPARγ and ST2 [57,58] but whether this is a sensing pathway for ILC2 in adipose tissue or other sites is yet unknown. It seems likely, however, that the ability of ILCs to finely sense metabolites would be critical to maintain tissue homeostasis.

Conclusions

Here we have outlined the parallels that exist between the innate and adaptive immune cells in their distribution and behavior. Collectively, they form a complex but highly synergistic network although key pieces of the puzzle that coordinate their regulation and interactions remain unknown. Progress on these elements will be essential to our understanding. Firstly, T_{RM} exhibit a distinct transcriptional profile but it is not yet known whether they arise from a distinct progenitor separate from effector and memory T cell lineages. Secondly, are tissue-resident lymphocytes replenished from local proliferation *in situ* or do they rely on circulating progenitors that can re-seed the interstitial compartments? In ILCs, proliferation has been thought to occur at a low rate within the tissues themselves leading to the idea that the numerical maintenance of the population occurs in isolation from circulating cells. This model, however, has been fortified by the paucity of evidence supporting circulating ILCs which has in part been blindsided by the lack of recognition that circulating cells may 'look' completely different from the mature populations. Thirdly, we need to think broadly about the identity of circulating precursors as they may not mimic the resident populations. Thus, a complete rethink of how we tackle resolving the elements of the tissue–tissue and tissue-vascular migratory pathways is warranted. Fourth, the factors that establish life-long maintenance in tissues, as opposed to long-term positioning followed by mobilization are poorly resolved. Whether these are similar or different for ILCs and T cells is not yet known, nor how collaboration is mediated between two distinctly different resident immune cell subsets. Fifth, while some key transcriptional regulators have been elucidated, the complete blueprint remains to be dissected. Transcription factor such as HOBIT, which is a key coordinator in the murine lineages, are differently expressed in human tissues suggesting it is not a master regulator. In addition, how the overlay of different tissue microenvironments modulates the transcriptional architecture remains to be uncovered. Addressing these and related questions are likely to shed new light on our understanding of the immune cell networks that protect our borders.

Conflict of interest statement

Nothing declared.

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