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Cardinal features of immune memory in innate lymphocytes

Endi K. Santosa[1,2], **Joseph C. Sun**[1,2]

[1]Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[2]Immunology and Microbial Pathogenesis Program, Weill Cornell Graduate School of Medical Sciences, Cornell University, New York, NY, USA.

Abstract

The ability of vertebrates to 'remember' previous infections had once been attributed exclusively to adaptive immunity. We now appreciate that innate lymphocytes also possess memory properties akin to those of adaptive immune cells. In this Review, we draw parallels from T cell biology to explore the key features of immune memory in innate lymphocytes, including quantity, quality, and location. We discuss the signals that trigger clonal or clonal-like expansion in innate lymphocytes, and highlight recent studies that shed light on the complex cellular and molecular crosstalk between metabolism, epigenetics, and transcription responsible for differentiating innate lymphocyte responses towards a memory fate. Additionally, we explore emerging evidence that activated innate lymphocytes relocate and establish themselves in specific peripheral tissues during infection, which may facilitate an accelerated response program akin to those of tissue-resident memory T cells.

The concept of 'immunological memory' predates our understanding of the vertebrate immune system. Long before Edward Jenner reported that milkmaids previously exposed to cowpox were protected against smallpox in 1798[1], the practice of inoculation to 'immunize' against an infection can be traced as far back as tenth-century China[2]. Since then, owing to the many discoveries that span several hundred years, we now appreciate the intricate molecular and cellular events constituting adaptive immunity that are critical for the generation of immunological memory. Nevertheless, in the past decade, the idea of immune memory being an exclusive trait of the adaptive immune system has been challenged by various studies demonstrating the existence of non-B-cell- and non-T-cell-mediated immune memory, thus blurring the line between innate and adaptive immunity.

Regardless of their innate or adaptive origins, immune memory cells must possess several cardinal features that explain their enhanced ability to provide protection compared to naive cells. First, the numerical abundance that results from clonal expansion provides quantitative strength to ensure that memory cells have a higher probability of encountering foreign

Correspondence and requests for materials should be addressed to Joseph C. Sun. sunj@mskcc.org.

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J.C.S. and E.K.S. contributed equally to all aspects of this article.

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invaders. Second, molecular adaptations through metabolic, epigenetic, and transcriptional reprogramming should 'poise' memory cells for a more rapid or robust effector response upon re-encountering a pathogen. And finally, tissue redistribution of memory cells positions them for an accelerated response against pathogens that breach the barrier surface. Together, these three features of—quantity, quality, and location—are interdependent and exquisitely shaped by early and highly coordinated priming events involving various cellular and molecular signals during the primary encounter with a pathogen.

In this Review, we discuss this newfound appreciation of an innate cell's ability to 'remember' previous insults that has reshaped our understanding of immunological memory, with a special focus on innate lymphocytes (natural killer (NK) cells and innate lymphoid cells (ILCs)). We will expand upon the three cardinal features of immune memory and highlight parallels between innate immune cells and their adaptive T cell siblings at the population level. We will provide an overview of the shared and distinct adaptive features that distinguish innate from adaptive memory, as well as the downstream molecular consequences of these processes that enhance their functionality. Last, we will discuss the emerging evidence that a commonality exists between tissue-resident innate memory cells and tissue-resident memory T cells. A broader understanding of how these responses are orchestrated will provide an opportunity to unleash the full potential of cellular and molecular components of immune memory.

Advantage of numerical abundance

Numerical abundance is one of the key factors in the memory cell's superior ability to respond to an infection compared with the naive cell. Naive T cells of a given epitope are incredibly sparse and must actively search for their cognate antigen before being primed in secondary lymphoid organs (SLOs) of the host by dendritic cells (DCs)—a mode of surveillance that is relatively slow and inefficient. By contrast, as a result of clonal expansion, memory T cells are much more abundant than naive T cells. When equipped with a greater number of epitope-specific memory T cells, the host enjoys a distinct advantage when re-encountering a pathogen, resulting in a much quicker, stronger, and focused surveillance.

As with T cells, certain innate lymphocytes are capable of clonal expansion, with the earliest and best-studied evidence originating from NK cell responses to mouse cytomegalovirus (MCMV)[3-5]. In this setting, engagement of the activating receptor Ly49H (encoded by *Klra8* and expressed by a subset of NK cells in C57BL/6 mice) with MCMV-derived glycoprotein m157 on infected cells[6,7] triggers selective clonal expansion of Ly49H$^+$ NK cells that has been measured to upwards of 10,000-fold compared to NK cells that failed to encounter MCMV-derived ligand[3,8] (Fig. 1). Moreover, akin to the subsequent contraction phase observed in their adaptive T and B cell siblings, many of these clonally expanded 'effector' Ly49H$^+$ NK cells undergo apoptosis following the acute phase of infection, leaving a pool of long-lived memory cells that can readily respond to reinfection[3]. Since these early studies, antigen-specific NK cell expansion has also been observed in the response of Rhesus macaques (*Macaca mulatta*) to simian immunodeficiency virus (SIV)[9], and in human responses to CMV (HCMV)[10-12] and malaria (*Plasmodium falciparum*)[13,14]. During

HCMV infection, the expansion of human NKG2C$^+$ NK cells is thought to be analogous to MCMV-specific Ly49H$^+$ NK cells in mice[10]. These 'adaptive' NKG2C$^+$ NK cells are clonal[15] and require HCMV UL-40-derived peptide, presented by non-classical HLA-E on HCMV-infected cells, to expand[16-19]. However, in the context of SIV and malaria, specific ligands and antigens or receptors involved in clonal expansion of NK cells have yet been clearly identified. The antigen-specific responses and clonal expansion described above are in stark contrast to the innate memory recently described in myeloid cells and non-immune cells, in which numerical advantage is not a factor in recall responses[20,21].

The interaction of Ly49H and m157 itself is required but alone is not sufficient to induce optimal clonal expansion of NK cells. Additional signals from other activating receptors are necessary for the expansion of these virus-specific NK cells, similar to the co-stimulatory signals required for robust expansion of virus-specific T cells[22]. In mice, interaction of DNAM-1 (encoded by *Cd226*) on NK cells with its ligands, CD155 and CD112 (expressed on splenic DCs and macrophages during infection), is needed for the optimal clonal expansion program of virus-specific Ly49H$^+$ NK cells (Fig. 1), through downstream signaling kinases Fyn and PKCη (ref. 23). Other receptors, such as NKG2D[24] and Ly49D[25] in mice, and CD2[26] in humans, may also support this clonal proliferation program.

In addition to these contact-dependent receptor signals, viral infection triggers a burst of proinflammatory cytokines that are instrumental for the adaptive program of virus-specific NK cells (Fig. 1). The induction of type I interferon (IFN) by plasmacytoid DCs[27-29], and likely by stromal[30] and myeloid cells[31], in response to MCMV is necessary to protect virus-specific NK cells from being killed by neighboring NK cells (a process called fratricide) through the STAT1–STAT2–IRF9 axis, but does not affect the clonal proliferation of Ly49H$^+$ NK cells[32]. At the same time, interleukin-12 (IL-12), produced by plasmacytoid DCs, classical DCs (cDC1s and cDC2s)[27,33], and monocytes[34], drives the innate effector program (for example, interferon-γ (IFNγ) secretion) and initiates many aspects of the adaptive features of NK cells by promoting cellular differentiation and proliferation in a STAT4-dependent manner[35]. Meanwhile, the production of IL-18 by cDC1s[36] amplifies IL-12 signaling[37], which in turn boosts IFNγ production and induces the expression of CD25 (the high-affinity chain of the IL-2 receptor) to mediate IL-2–STAT5-driven expansion of virus-specific NK cells[38]. Thus, in many ways, the signals that are required to initiate the clonal expansion program in NK cells parallel those of T cells[39]. Although we are beginning to understand the contribution and integration of these individual signals[40], it remains unclear how they are coordinated in vivo in the context of inflamed or infected tissues.

Along these lines, exactly when and where do antiviral NK cells encounter these signals? Much like naive T cells that are retained in the SLO after antigen engagement, naive NK cells similarly abandon their nomadic lifestyle upon encountering an antigen during viral infection. Early after MCMV infection, Ly49H$^+$ NK cells likely encounter virally infected cells in the red pulp and migrate into the white pulp through the marginal zone[41-45], where they then interact with cDC1s[36], presumably through an XCL1–XCR1-axis[46]. Whether these interactions provide some or all of the critical signals that initiate the adaptive

program of virus-specific NK cells remains unclear. Interestingly, within the white pulp, neuro–immune crosstalk between Ly49H$^+$ NK cells and adrenergic neurons has recently been suggested to support the optimal expansion of virus-specific NK cells[47]. Thus, as with T cells, NK cells may need to be primed in SLOs during infection, although the contribution of splenic-specific priming events towards the overall systemic expansion of NK cells and the generation of memory remains to be determined.

This phenomenon poses the question of whether the priming of the adaptive NK cell program is exclusive to SLO sites such as the spleen, or whether priming can occur and/or be initiated in peripheral organs. Indeed, recent studies have suggested that naive T cells can be primed outside of the SLOs, namely in the liver[48,49] and the vaginal mucosa[50]. Moreover, there are examples in which priming of other ILCs in peripheral tissues resulted in clonal or clonal-like expansion (Fig. 1). For instance, liver ILC1s can expand and form memory in an antigen-dependent manner during MCMV infection[51]. Because ILC1s do not express Ly49H-like NK cells, this process is mediated by the interaction of the activating receptor NK1.1 on liver ILC1s and MCMV-derived protein m12 (refs. 51,52). Notably, both NK cells and ILC1s express NK1.1, and thus it remains unclear to what extent the NK1.1–m12 interaction contributes towards the adaptive features of ILC1s versus NK cells. Other members of the ILC family, namely ILC2s in the lung and ILC3s in the small intestine, have also been recently shown to possess these adaptive features (Fig. 1). Distinct from the antigen-dependency of their group 1 innate lymphoid siblings, ILC2 expansion in the lung is primarily driven by the cytokine IL-33, which is induced by the allergen papain, or *Aspergillus*[53,54]. Furthermore, ILC3s can also mount a secondary response following *Citrobacter rodentium* challenge[55]. Interestingly, the expansion of ILC3s is not pathogen-specific and requires signals beyond IL-1β and IL-23 as treatment with these cytokines alone in the absence of infection failed to induce memory responses. Thus, the additional signals required to induce ILC3 memory remain an open question. Collectively, these findings suggest that clonal or clonal-like expansion is a conserved trait of all ILCs that provides them with a numerical advantage for heightened protection against secondary infection. Whether in certain settings this expansion may actually represent a maladaptation that drives unwanted inflammation at tissue sites and causes diseases (for example, asthma, inflammatory bowel diseases, or psoriasis) remains to be better understood[54,56,57].

Triad of molecular adaptations

Clonal expansion not only serves as a way to produce many memory cells, but also acts as a vehicle for molecular adaptation that endows a select number of long-lived cells to participate in memory responses with heightened functionality, in part owing to the selection of high-affinity and high-avidity cells[58,59]. Notably, the process of clonal expansion itself is not a prerequisite for molecular adaptation. At the heart of this qualitative difference between naive versus memory cell lies the complex interplay between metabolism, epigenetics, and transcription (Fig. 2). Metabolic reprogramming of antigen-activated lymphocytes provides necessary fuel sources for taxing cellular processes, including epigenetic modifications and transcription, that consequently can modulate additional metabolic pathways by regulating the epigenetic landscape and the expression

of metabolic and other important genes, representing both feedback and feed-forward mechanisms.

During activation and clonal expansion, both NK cells and T cells experience substantial metabolic reprogramming to sustain the substrate demand for proliferation as well as differentiation[60]. For instance, although naive $CD8^+$ T cells primarily rely on oxidative phosphorylation (OXPHOS) for their homeostasis, they shift towards glycolysis and amino acid metabolism (Fig. 2), including glutaminolysis, during activation and differentiation into effector cells[63-65], similar to activated NK cells[66,67]. Deletion of a component of lactate dehydrogenase, the rate-limiting enzyme that mediates the conversion of pyruvate into lactate, is detrimental to both NK cell and $CD8^+$ T cell expansion[66], possibly in part owing to the direct regulation of the cell cycle by lactate itself[68]. However, distinct signals appear to drive the metabolic switch in these cell types, specifically the triggering of the T cell receptor (TCR) and the co-stimulatory molecule CD28 in $CD8^+$ T cells, and the proinflammatory cytokines sensed by NK cells[61,66,69]. The transcription factor MYC plays a critical role in this metabolic shift by controlling the expression of metabolic enzymes and nutrient transporters, such as GLUT1 and amino acid transporters, to satisfy nutrient demands for cell division and protein synthesis[70]. This metabolic shift in turn regulates the levels of MYC itself through mTOR signaling and the sensing of endoplasmic reticulum stress[67,69,71]. Moreover, whereas glutaminolysis acts as an alternative carbon source by breaking down glutamine to fuel the tricarboxylic acid (TCA) cycle in the form α-ketoglutarate (α-KG) in T cells[69], this process seems to play a minimal role in maintaining OXPHOS in cytokine-activated NK cells[67]. Instead, NK cells require the transcription factor hypoxia-inducible factor 1-α for optimal glucose metabolism to support the survival of virus-specific NK cells[72] and the effector functions of tumor-infiltrating NK cells[73].

In contrast to activated and effector cells, several studies have reported that memory $CD8^+$ T cells are more dependent on fatty-acid oxidation[74] rather than glycolysis—a feature shared with memory ILC3s[55]. Indeed, deletion of a glycerol transporter or enzymes involved in triglyceride synthesis and storage results in impaired survival of memory $CD8^+$ T cells[75]. However, genetic deletion of the fatty-acid transporter CPT1A, the rate-limiting enzyme of fatty-acid oxidation, in $CD8^+$ T cells had no effect on memory cells. This is in contrast to studies that have used the pharmacological inhibitor of CPT1A, etomoxir; thus, highlighting CPT1A-independent off-target effects by etomoxir that may explain this discrepancy[76]. Whereas other metabolic traits, such as mitochondrial biomass and spare respiratory capacity, are also increased in memory $CD8^+$ T cells compared with their naive counterparts[77], memory $Ly49H^+$ NK cells exhibit a lower number of mitochondria and higher mitochondrial membrane potential compared to naive NK cells[78]. Similarly, human adaptive NK cells also exhibit higher mitochondrial membrane potential and OXPHOS that is seemingly mediated by the chromatin-modifying enzyme ARID5B[79]. It is very likely that other memory ILCs experience distinct types of metabolic remodeling, because even myeloid populations that exhibit ‘memory-like’ responses have been shown to undergo metabolic rewiring[80-82].

The metabolic rewiring of $CD8^+$ T cells and NK cells during viral infection not only fulfills their energy and nutrient demands, but also mediates epigenetic reprogramming

that facilitates optimal function and differentiation. Metabolic intermediates can act as substrates for epigenetic modifications, as well as regulators of epigenetic enzyme activity (Fig. 2). For instance, acetyl-CoA, a metabolite derived from carbohydrates, fatty acids, and amino acid catabolism, acts as a substrate for histone acetylation by the histone acetyltransferases (HATs), including p300 and CBP, in addition to its role as a fuel source for the TCA cycle[83]. Similarly, the catabolism of the amino acid methionine results in the production of *S*-adenosylmethionine (SAM), a universal methyl-donor for nucleotide and histone methylation[84], whereas the byproduct of glutaminolysis, α-KG, regulates enzyme activities that promote demethylation[85]. As such, disruption of some of these key metabolic pathways can immensely impact the epigenetic landscape and functions of a variety of cell types. Moreover, there are many examples of histone modifications mediated by metabolic intermediates that have recently been discussed elsewhere[86].

Naive $CD8^+$ T cells possess epigenetic features of 'quiescence' that are distinct from those of effector and memory cells, which may explain the distinct levels of responsiveness between these differentiation states. Histone profiling of differentiating $CD8^+$ T cells suggests that many regulatory regions associated with loci of key factors critical for effector and memory fates, such as the transcription factors *Tbx21* (which encodes T-bet), *Id2*, and *Id3*, among others, are kept in a 'bivalent' state in naive $CD8^+$ T cells in which they are marked by the specific histone marks trimethylated histone H3 K4 (H3K4me3) and H3K27me3, but not acetylated H3 K27 (H3K27ac), which are indicative of a poised but inactive transcriptional state[87,88]. Upon activation, naive $CD8^+$ T cells experience substantial epigenetic reprogramming that coincides with changes in metabolic programs[89]. For example, blocking pyruvate transport into the mitochondria for acetyl-CoA conversion impairs effector T cell differentiation while paradoxically promoting memory generation by altering metabolic pathways that affect the availability of acetyl-CoA for histone acetylation[90]. Disruption of other metabolic enzymes, including lactate dehydrogenase, may similarly affect T cell fate, in part through epigenetic mechanisms[65,91]. Meanwhile, deletion of a component of p300/CBP results in the loss of the naive cell's ability to expand and differentiate into effector and memory cells[92], whereas inhibition of EZH2 (refs. 93,94) or SUV39H1 (ref. 95), which methylate H3K27 and H3K9, respectively, selectively impairs effector, but not memory, differentiation. Together, these studies underscore the importance of active epigenetic regulation by metabolic pathways and epigenetic enzymes in promoting optimal cytotoxic lymphocyte responses to infection.

Much like $CD8^+$ T cells, NK cells also undergo significant epigenetic remodeling in response to viral infection[96]. These changes are primarily induced by proinflammatory cytokine signals early after infection that result in a distinct yet coordinated epigenetic reprogramming of NK cells (Fig. 2). During MCMV infection, type I IFN signaling through its downstream transcription factor STAT1 triggers chromatin modifications at gene promoters, in part through deposition of H3K4me3 (ref. 40). The specific mechanisms by which STAT1 mediates this promoter-centric chromatin remodeling are not entirely clear but may be due to preferential binding of STAT1 to promoter regions, which affects the ability of the MLL complex to methylate H3K4 in these regions[96]. By contrast, the IL-12–STAT4 axis predominantly remodels enhancers by acting as a pioneering factor to prime de novo enhancers through induction of chromatin accessibility and recruitment of p300/CBP for

H3K27 acetylation, as deletion of STAT4 results in loss of enhancer accessibility as well as p300 binding[40,96,97]. Moreover, IL-12–STAT4-mediated chromatin remodeling may be enhanced by the synergistic cooperation between IL-12 and the IL-18–NF-κB and IL-2–IL-15–STAT5 axes[40], signals known to be critical in driving both innate and adaptive features of NK cells. However, little is known about how antigen receptor signaling, along with co-stimulatory receptor triggering, impacts chromatin remodeling—all of which could potentially be driven by the crosstalk of NFAT, NF-κB, and/or AP-1 factors.

Whereas the early cytokine-driven histone remodeling of NK cells is becoming better understood, much less is known about the regulation of epigenetic reprogramming during their differentiation in vivo throughout the course of an infection. Naive NK cells possess significant epigenetic and transcriptomic features (likely acquired during their development and education)[98] that bear striking resemblance to memory $CD8^+$ T cells, as assessed by chromatin accessibility[96]. Furthermore, memory $Ly49H^+$ NK cells and adaptive $NKG2C^+$ NK cells are enriched in AP-1 footprints compared with their naive counterparts[15,96], a feature that may be imprinted early following antigen-receptor engagement. Importantly, this AP-1 footprint is a common epigenetic signature that is shared with not only memory $CD8^+$ T cells, but also other types of memory cells[99]. AP-1 itself is a critical factor for cell-type-specific enhancer selection through its interaction with other transcription factors and the chromatin-remodeling SWI/SNF complex[100], and has recently been implicated in shaping the three-dimensional (3D) enhancer landscape[101]. Notably, in $CD4^+$ T cells, AP-1-mediated 3D chromatin remodeling has been reported to be dependent on ETS-mediated recruitment of CTCF[102,103]. Our own analysis of the 3D chromatin structure of differentiating MCMV-specific $CD8^+$ T cells and $Ly49H^+$ NK cells also suggests that AP-1 factors are involved in mediating dynamic changes in the genome architecture during the transition from naive to memory cells in these two cell types[104]. Thus, the rapid responsiveness of memory cells across different cell types may be explained by the shared epigenetic identity imparted through the cooperation between transcription factors and chromatin organizers.

The intricate relationship between transcription factors and epigenetic remodeling facilitates the expression and/or binding of other transcription factors that regulate cellular differentiation, function, and phenotype (Fig. 2). Both NK cells and $CD8^+$ T cells share many transcriptional programs, including those mediated by the T-box family of transcription factors, T-bet and EOMES, which are indispensable for the development of NK cells and the maintenance of memory $CD8^+$ T cells[105-107]. ILC1 development is similarly dependent on T-bet, but not EOMES[108]. Other transcription factors that control effector and memory fates of $CD8^+$ T cells, such as BACH2[109], ZEB2[110], BLIMP-1[111], ID2[112], and TCF7[113], also regulate NK cell maturation at steady state[109,114-119], further highlighting a shared transcriptional program between these innate and adaptive cytotoxic lymphocytes. Interestingly, a master transcription factor of T cell identity, BCL11B, has been shown to be similarly critical for adaptive NK cell differentiation in humans and mice[120].

During infection, the transcriptional circuitries that govern virus-specific NK cells and $CD8^+$ T cells also exhibit a high degree of overlap, as highlighted by the shared requirement of STAT transcription factors for the optimal responses of these sibling lymphocytes, and may involve complex interplay between additional lineage-defining and signal-driven

transcription factors[97,121]. Antigen receptor triggering in T cells induces an AP-1-dependent transcriptional program through the cooperation of AP-1 with interferon regulatory factor 4 (IRF4), which may be regulated by the affinity of antigen–receptor interactions[122,123], and this cooperative interaction has a critical role in controlling the transcription-factor network that is essential for T cell subset differentiation[122-126]. Importantly, AP-1 family members (such as BATF) also act as pioneering factors that shape the chromatin landscape of activated T cells, although this activity is independent of IRF4[103]. It is unclear whether an affinity- or avidity-dependent transcriptional program exists in NK cells[18,59]. In contrast to T cells, in which IRF4 expression is triggered by antigen receptor signaling, the expression of IRF4 in MCMV-specific NK cells relies on the synergistic cooperation between activating receptor and proinflammatory cytokine signals. Our recent study provides evidence that the transcriptional program orchestrated by IRF4 is critical for the survival and the differentiation of virus-specific NK cells in part by regulating nutrient uptake essential for the adaptive NK cell response[127].

Notably, NK cells at steady state do express IRF8, which shares significant homology with IRF4 and can partner with AP-1 factors[128]. During infection, IRF8 can be further induced in NK cells by IL-12 and IL-18, and IRF8-deficient Ly49H$^+$ NK cells failed to expand owing to their inability to upregulate ZBTB32, a cell cycle regulator that promotes proliferation by suppressing BLIMP-1 in NK cells[129,130]. Whether IRF8-mediated induction of ZBTB32 is dependent on AP-1 factors is yet to be determined. In addition to its regulation of the IRF8–ZBTB32 arm, the IL-12–STAT4 program is also required for the induction of RUNX family members, namely RUNX1 and RUNX3, which along with CBFβ support the proliferation program of MCMV-specific Ly49H$^+$ NK cells for optimal generation of memory[131]. Although the mechanism by which RUNX factors orchestrate this process in NK cells is unclear, RUNX3 in CD8$^+$ T cells appears to function through both transcriptional and epigenetic mechanisms[132-134]. Furthermore, although less is known about the transcriptional regulation for the maintenance of memory NK cells, both memory NK cells and CD8$^+$ T cells depend on the cytokine IL-15 and its downstream transcription factor STAT5 for their survival[135]. Altogether, the intimate crosstalk between metabolism, epigenetics, and transcription orchestrates the cell-intrinsic qualitative differences that render memory cells superior to naive cells in the host defense against pathogens.

Convenience of tissue redistribution

A major immunosurveillance mechanism of NK cells and CD8$^+$ T cells relies on the identification and elimination of infected or transformed target cells. As such, the continuous patrolling of these cytotoxic lymphocytes provides an effective, yet relatively delayed, mode of surveillance. As previously discussed, naive CD8$^+$ T cells must be primed in SLOs such as lymph nodes, undergo clonal expansion, and then be actively recruited to infected or inflamed peripheral tissues—a lengthy and taxing process that may take several days to complete. Although the speed of the response is faster for NK cells because of their ability to execute innate effector functions without pre-sensitization, they still need to actively migrate from the blood into the affected tissues before eliminating infected cells.

In recent years, many studies have highlighted the ability of memory T cells to adapt and reside in tissues for extended periods of time. This ability is a convenient mechanism for the host to provide immediate protection at sites of pathogen entry, as these tissue-resident memory T (T_{RM}) cells can quickly respond to local infection without having to migrate[136]. Thus, the capacity of T_{RM} cells to persist outside of lymphoid organs is analogous to the ability of ILC1s, ILC2s, and ILC3s (helper ILCs) to preferentially inhabit peripheral tissues. Importantly, although both T_{RM} and helper ILCs are tissue-resident lymphocytes that provide local immune protection, helper ILCs arise early during organism development, seed the tissues, and maintain their identity through self-renewal and proliferation[137], whereas T_{RM} cells originate from activated T cells primed in the SLO and have subsequently traveled through circulation into tissues[136]. However, there are studies that have described the mobilization of ILC2s from other tissues that subsequently acquire residency in the lung upon infection[138,139] (Fig. 3). Nevertheless, despite their distinct ontogeny and mechanisms of tissue recruitment and seeding, T_{RM} cells and helper ILCs share many features, including their dependency on the transcription factors Hobit[33,140] and T-bet[108,141], among others.

The ability to establish tissue residency is not just a characteristic of helper ILCs and T_{RM} cells, but is also a feature of circulating NK cells. A couple of recent studies have suggested that MCMV infection drives clonal expansion of spleen-resident NK cells and promotes the recruitment of NK cells that reside long-term in the salivary gland and the lungs[46,142]. Notably, CMV infection in both mice and humans results in virus latency, and CMV hides within organs including the salivary gland, where it can be reactivated and shed[143,144]. Thus, it is unclear whether the initial long-term retention of NK cells in these tissues is driven by the need to continuously control the virus. Although one study has proposed that these tissue-resident NK cells aid the rapid activation of $CD8^+$ T cells by facilitating T–DC interactions during viral infection, another suggests that these NK cells remain in the tissue after viral clearance to limit pathology mediated by $CD4^+$ T cells[46,142]. Moreover, the recruitment and residence of long-lived NK cells in tissue have not only been observed in systemic MCMV infection, but also during acute local skin infection with Vaccinia virus or *Staphylococcus aureus*, with tissue-resident NK cells exhibiting a distinct transcriptional profile from that of circulating NK cells, and mediating an accelerated effector response upon reinfection (unpublished observations, Torcellan and Gasteiger) (Fig. 3).

Many exciting questions remain to be resolved regarding memory in innate lymphocytes from peripheral tissues. For instance, does the priming of tissue-resident NK cells first occur in situ or elsewhere? How are tissue-resident memory innate lymphocytes first recruited into the tissues, and what are the signals required for the recruitment or residency program? Are there specific roles for tissue-resident NK cells and other memory ILCs during tissue homeostasis and/or local infection? What are the metabolic, epigenetic, and transcriptional programs that drive tissue residency of NK cells and other memory ILCs, and are these programs conserved or distinct across different tissues? Finally, what transcription factors maintain the identity of tissue-resident memory ILCs, and are these factors and programs shared with T_{RM} cells? Importantly, tissue-resident signatures have also been observed in NK cells isolated from various human tissues and have been associated with positive clinical outcomes, suggesting that there is a conserved tissue-residency program within ILCs across species that may contribute to individual fitness[145,146].

Concluding remarks

We now appreciate that innate immune cells possess characteristics that were previously thought to be exclusive to the adaptive immune system. Exciting efforts to harness the memory properties of innate lymphocytes have shown promising results in the clinic, as in the case of bone marrow transplantation or in treatments for various malignancies[147-151]. Although current endeavors using the memory properties of ILCs have been somewhat limited to cytokine-induced memory-like NK cells, other NK-cell-based therapeutics, including chimeric antigen receptor NK cells and NK cell engagers, may benefit from exploiting the adaptive features of NK cells[152,153].

Beyond utilizing NK cells in the clinic, harnessing helper ILCs could improve strategies for anti-tumor immunity as well. However, the role of helper ILCs in malignancy is still unclear, with emerging studies only beginning to unravel their complex interactions with the tumor microenvironment[154]. Whether the memory features of helper ILCs can be harnessed to improve anti-tumor immunity in a context-dependent manner requires further investigation but holds potential for future therapeutics. As we continue to explore the cellular and molecular mechanisms that govern these adaptive features and transition from population-level approaches to the single-cell level, we hope to unravel new complexities and gain a more nuanced understanding of the intricate workings of the innate and adaptive immune system, with the ultimate goal of developing new therapies or immunization strategies to combat infectious diseases and other pathologies.

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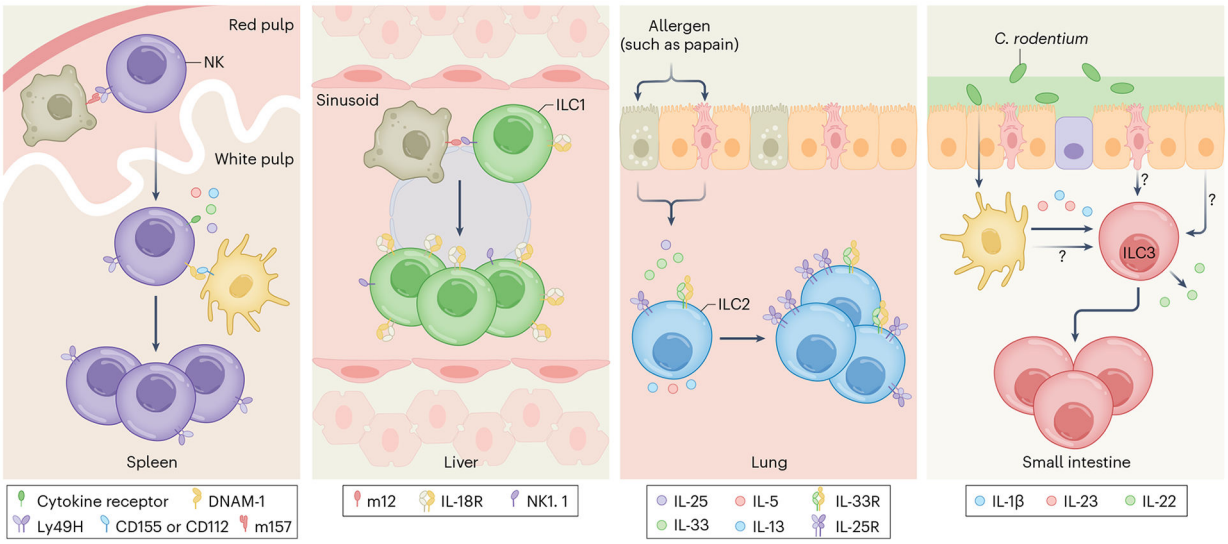

Fig. 1 | Advantage of numerical abundance.

Clonal or clonal-like expansion equips memory cells with a quantitative advantage to quickly respond to secondary infections, in part by increasing the probability of encountering pathogens. For naive splenic Ly49H^{+} NK cells, signals from engagement of the activating receptor by MCMV-infected cells (gray cells) and co-stimulatory molecules as well as proinflammatory cytokines from myeloid cells (yellow cells) are necessary for clonal expansion (first panel). In the liver, interaction between activating receptor NK1.1 and the MCMV-derived viral ligand m12, expressed by infected cells, initiates clonal-like expansion of ILC1s (second panel). Meanwhile, ILC2s and ILC3s undergo clonal-like proliferation in an antigen-independent manner. Lung ILC2s require the cytokine IL-33, which is released by epithelial cells upon papain challenge (third panel), whereas the expansion of small intestinal ILC3s by *C. rodentium* are induced by IL-1β, IL-23, and other unidentified signals (fourth panel).

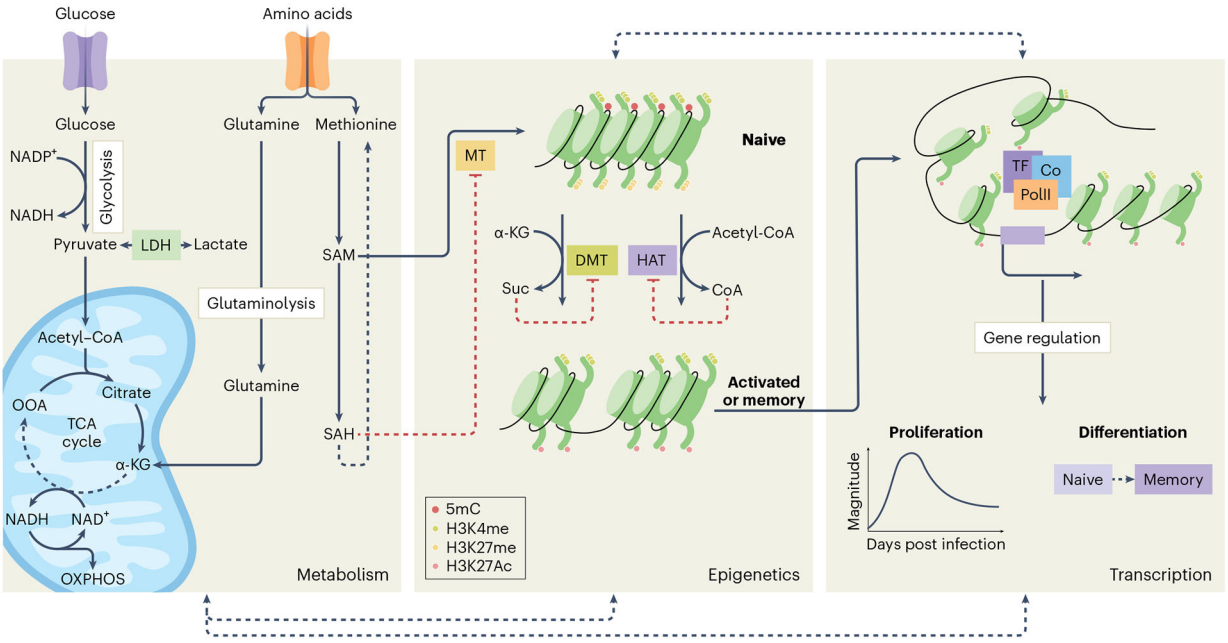

Fig. 2 | Triad of molecular adaptations.

The complex interplay between metabolism, epigenetics, and transcription primes memory cells for qualitative advantages over naive cells. Upon activation, a metabolic shift provides lymphocytes with the necessary fuels for epigenetic modifications that facilitate transcription of genes required for proliferation, differentiation, and effector function. For instance, acetyl-CoA is a substrate for histone acetylation, facilitated by histone acetyltransferases (HAT), whereas SAM is a universal methyl-donor for histone and/or DNA methyltransferases (MT). *S*-adenosylhomocysteine (SAH), a SAM byproduct, negatively regulates the activity of MTs, whereas α-KG promotes demethylation by histone and/or DNA demethylases (DMT). Altogether, this intimate crosstalk lowers the cell-intrinsic molecular activation threshold in memory cells, in part through phenotypic changes. As a result, memory cells are better equipped to respond more rapidly and robustly to secondary infection than naive cells. LDH, lactate dehydrogenase; OOA, oxaloacetate; suc, succinate; TF, transcription factor.

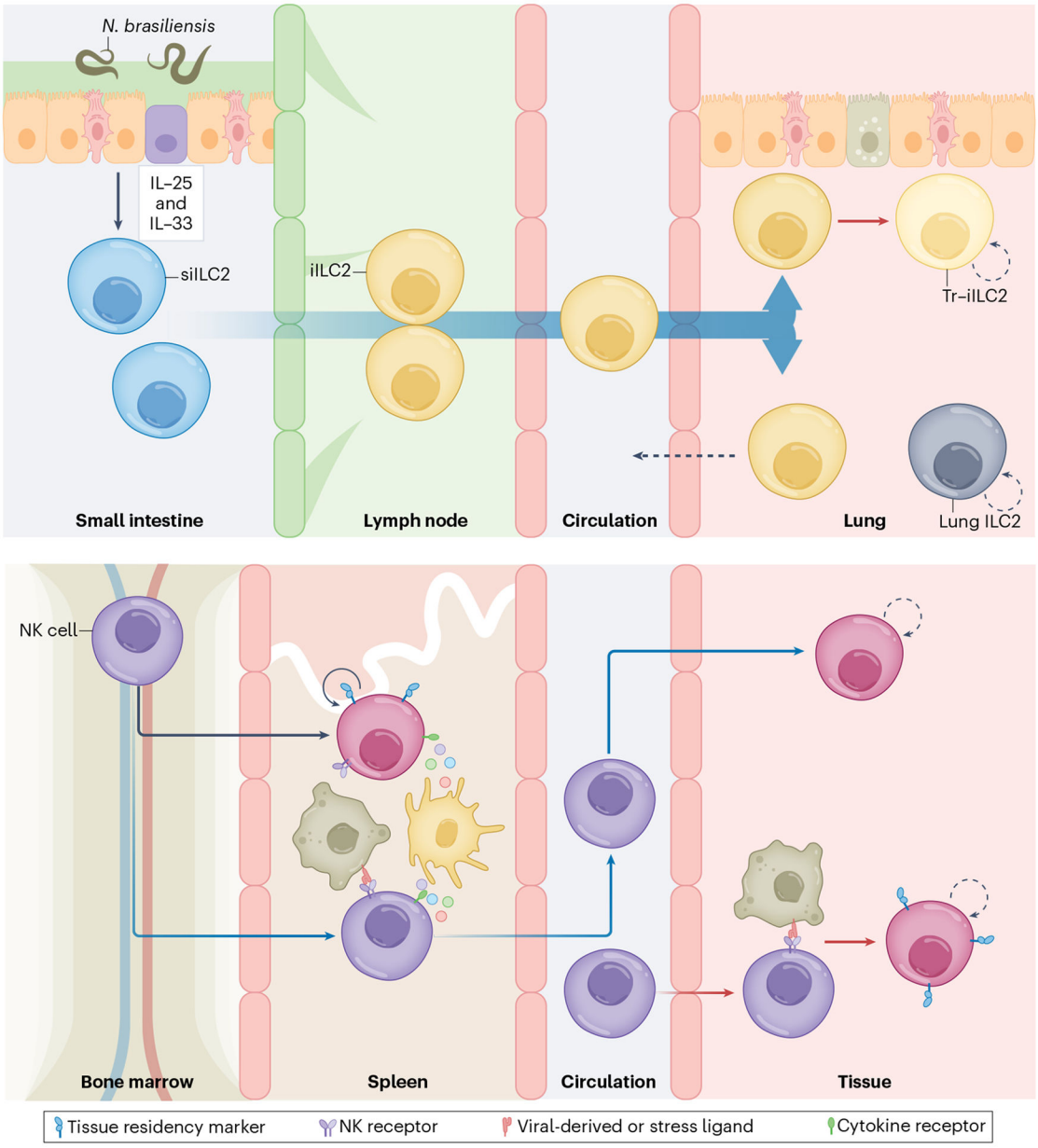

Fig. 3 | Convenience of tissue redistribution.

The ability of memory cells to reside in tissues facilitates an accelerated immune response at the site of pathogen entry without having to migrate. Top, small-intestine ILC2s (siILC2s) have been shown to differentiate and migrate into the lung in response to *Nippostrongylus brasiliensis* in a sphingosine-1-phosphate-dependent manner (blue gradient). A small fraction of these iILC2s then stays in the lung (Tr-iILC2s) and co-exists with lung ILC2s, whereas other iILC2s migrate back into the small intestine. Bottom, in addition to tissue-resident helper ILCs, splenic-tissue-resident NK cells that contribute to the MCMV-specific response have been described (black arrow). Furthermore, although other tissue-resident NK cells can be generated in response to MCMV and other infections, it is unclear whether they

are primed elsewhere, such as SLOs (blue arrow), or in the tissues in which they ultimately reside (red arrow).