



## REVIEW ARTICLE

## Innate lymphoid cell memory

Xianwei Wang<sup>1,2</sup>, Hui Peng<sup>1,2</sup> and Zhigang Tian<sup>1,2</sup>

Innate lymphoid cells (ILCs), including natural killer (NK) cells, ILC1s, ILC2s, ILC3s, and lymphoid tissue inducer (LTi) cells, comprise the first line of innate immune defense against pathogens and tumors. Over the past decade, accumulating evidence has demonstrated immunological memory in ILC subsets: for example, NK cells recall haptens, viruses, and cytokines; ILC1s recall haptens; and ILC2s recall cytokines. Although the development and functions of ILCs mirror those of T-cell subsets, ILC and T-cell memory exhibit both common characteristics and specific properties. Encouragingly, ILC memory has been found to confer benefits in long-term tumor control and vaccination, providing insight for novel memory ILC-based tumor immunotherapy and vaccine-development strategies. In this review, we discuss the evidence supporting ILC memory and present a comprehensive framework of the ILC memory system.

*Cellular & Molecular Immunology* (2019) 16:423–429; <https://doi.org/10.1038/s41423-019-0212-6>

## INTRODUCTION

Members of the innate lymphoid cell (ILC) family, composed of natural killer (NK) cells, ILC1s, ILC2s, ILC3s, and lymphoid tissue inducer (LTi) cells, functionally mirror their adaptive counterparts, CD8<sup>+</sup> and CD4<sup>+</sup> T-cell subsets.<sup>1–4</sup> ILCs provide the first line of host immune defense against pathogenic infection and tumor development. Specifically, NK cells produce perforins, granzymes, and interferon (IFN)- $\gamma$  in response to viruses and tumor cells. Like Th1 cells, ILC1s produce IFN- $\gamma$  and tumor necrosis factor (TNF) during viral and bacterial infections.<sup>5–7</sup> ILC2s combat parasitic invasions and participate in allergic inflammation via the production of type 2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13.<sup>8,9</sup> ILC3s mediate innate immune responses against extracellular bacteria and fungi through the production of IL-17 and IL-22.<sup>10–13</sup> LTi cells are critical for lymph node (LN) development in a lymphotoxin-dependent manner.<sup>14</sup> Due to their lack of recombination-activating genes (RAGs), ILCs cannot express diverse rearrangement-mediated antigen-recognition receptors and have thus been traditionally defined as innate immune cells capable of mounting rapid responses in the absence of prior sensitization.

Immunological memory is a hallmark of adaptive T and B cells. Upon exposure to antigens, adaptive lymphocytes carrying specific receptors undergo expansion and contraction, eventually acquiring memory potential. Upon encountering the same antigen, adaptive lymphocytes with specific memory mediate robust recall responses. Over a decade ago, von Andrian and colleagues found that not only T and B cells but also NK cells are capable of mediating adaptive contact hypersensitivity responses (CHS).<sup>15</sup> Since then, memory NK cells recognizing mouse cytomegalovirus (MCMV),<sup>16</sup> cytokines,<sup>17</sup> simian immunodeficiency virus (SIV),<sup>18</sup> and human cytomegalovirus (HCMV)<sup>19</sup> have been reported in mice, rhesus macaques, and humans. NK cell memory capabilities have since become widely appreciated. Interestingly, recent studies have further revealed the memory features of

ILC1s<sup>20</sup> and ILC2s.<sup>21</sup> These new findings have greatly contributed to our understanding of immunological memory and have extended the concept of NK cell memory to ILC memory. In this review, we summarize the advances and present a comprehensive framework of ILC memory.

## MEMORY NK CELLS

## Memory NK cells in inflammation

The first evidence supporting ILC memory came from a study by the von Andrian laboratory.<sup>15</sup> The CHS model is a well-established mouse model for human allergic contact dermatitis (ACD), in which adaptive T cells are considered responsible for allergic inflammation. Unexpectedly, von Andrian and colleagues found that CHS responses could also be induced in *Rag1*<sup>-/-</sup>, but not *Rag1*<sup>-/-</sup>*γc*<sup>-/-</sup> mice, and that sensitized liver NK cells, but not splenic NK cells, could transfer immunological memory to naive mice.<sup>15</sup> *Rag1*<sup>-/-</sup> mice vaccinated with influenza virus strain A/PR/8/34 (PR8), vesicular stomatitis virus, and human immunodeficiency virus type 1 were found to exhibit prolonged survival upon specific viral challenges,<sup>22</sup> underscoring the prospective use of memory NK cells in novel vaccine-development strategies. The chemokine receptor CXCR6 plays a key role in the homeostasis of antigen-specific memory NK cells, as evidenced by the findings that liver CXCR6<sup>+</sup> NK cells can mediate long-term memory responses and that *Rag1*<sup>-/-</sup>*Cxcr6*<sup>-/-</sup> mice fail to mount CHS responses.<sup>22</sup> The “liver-restriction” feature of hapten-specific memory NK cells was not explained until the discovery of CD49a<sup>+</sup> liver-resident NK cells. Liver NK cells are heterogeneous populations composed of CD49a<sup>+</sup> liver-resident NK cells and CD49b<sup>+</sup> conventional NK (cNK) cells.<sup>23</sup> CD49a<sup>+</sup> liver-resident NK cells do not circulate throughout the body, and these cells account for nearly half of all liver NK cells.<sup>23–25</sup> In recent years, great advances have been made in studying the tissue residency

<sup>1</sup>Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, The CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei 230027 Anhui, China and <sup>2</sup>Institute of Immunology, University of Science and Technology of China, Hefei 230027 Anhui, China

Correspondence: Zhigang Tian (tzg@ustc.edu.cn)

Received: 22 December 2018 Accepted: 27 January 2019

Published online: 22 February 2019

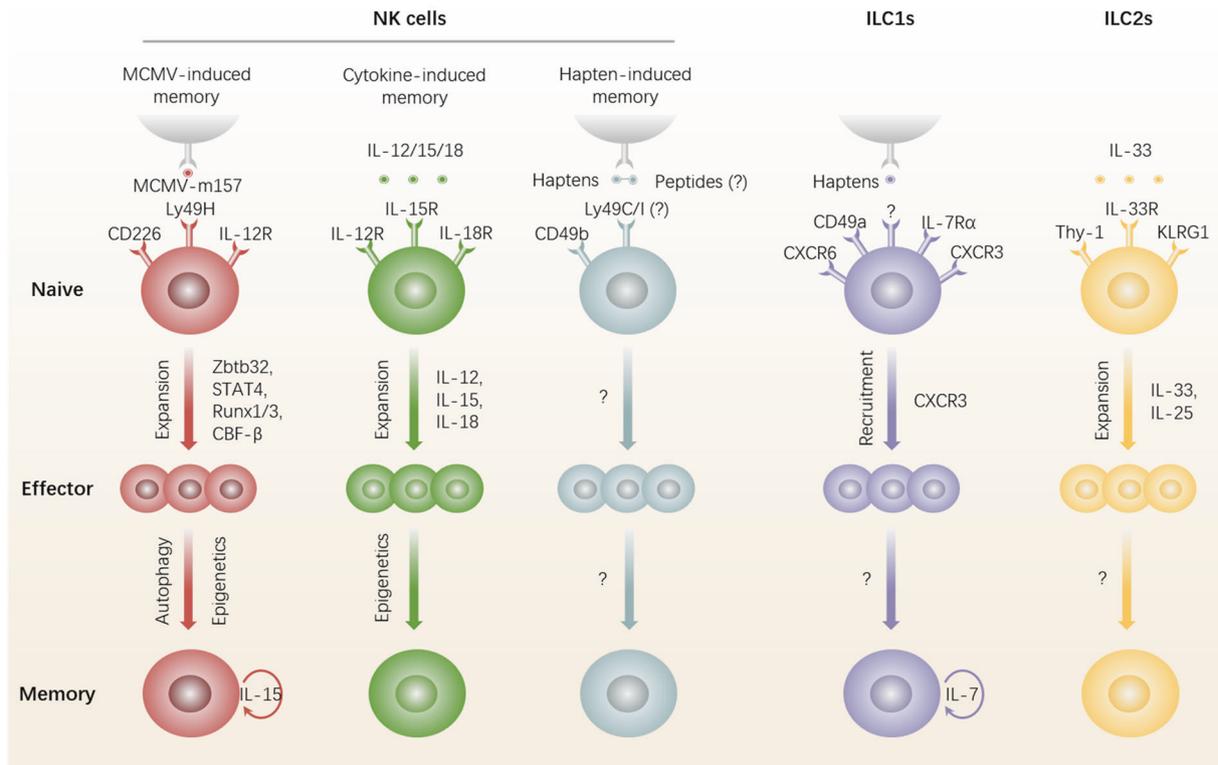
of lymphocytes, and CD49a has been accepted as a classical marker of tissue residency.<sup>26,27</sup> Although CD49a<sup>+</sup> liver-resident NK cells exhibit cytotoxic activity,<sup>28</sup> this subset is also referred to as liver ILC1s, as they lack the transcription factor Eomes and differ from cNK cells in their progenitor origin.<sup>6,26,29,30</sup> CD49a<sup>+</sup> liver-resident NK cells express high levels of CXCR6,<sup>23</sup> a key regulator of hapten-specific memory NK cells. Adoptive transfer experiments have demonstrated the memory features of CD49a<sup>+</sup> liver-resident NK cells.<sup>23</sup> In aryl hydrocarbon receptor-deficient mice, CD49a<sup>+</sup> liver-resident NK cells were found to have reduced numbers and lack the ability to mediate hapten-specific memory responses.<sup>31</sup>

In addition, CD49b<sup>+</sup> cNK cells have also been reported to mediate CHS responses (Fig. 1). Pro-hapten monobenzene-induced CHS is primarily driven by memory cNK cells.<sup>32</sup> Inflammasome activation in macrophages and the downstream cytokine, IL-18, are required for memory cNK cell formation in this model.<sup>32</sup> As monobenzene is metabolized in melanocytes to generate haptens, monobenzene-induced memory cNK cells display specific cytotoxicity against melanocytes, efficiently controlling B16 tumor development.<sup>32</sup> A recent study has reported that the complete deficiency of Ly49 family member receptors results in the failure to induce CHS, and a knock-in of Ly49I restores liver NK cell-mediated dermal inflammation, suggesting that educated NK cells have the potential to acquire immunological memory.<sup>33</sup> Surprisingly, Ly49C/I

I-sensitive peptides have been found to induce NK-cell recall responses,<sup>33</sup> implying that haptens may form complexes with self-proteins containing Ly49C/I-sensitive peptides and that liver NK cells may directly recognize such complexes. In this case, however, it remains unclear how the germline gene encoding Ly49 receptors discriminates among different hapten-self-protein complex structures, the specificities of which are determined by self-proteins. Understanding the mechanisms of antigen recognition remains the greatest challenge in the study of hapten-induced memory NK cells. The reason why Ly49C/I-dependent memory NK cells are liver restricted also remains to be elucidated. Given that Ly49C/I is highly expressed on circulating NK cells but minimally expressed on CXCR6<sup>+</sup> NK cells,<sup>20</sup> there must be other key factors responsible for liver-restricted memory-cell generation. Because CD49b<sup>+</sup> cNK cells lack CXCR6 expression, a CXCR6-independent mechanism may be involved in Ly49C/I-mediated memory NK-cell formation. Collectively, the two parallel systems of CD49a<sup>+</sup>CXCR6<sup>+</sup> liver-resident NK cells and CD49b<sup>+</sup>Ly49C/I<sup>+</sup> cNK cells may be responsible for the development of hapten-induced liver-restricted immunological memory.

#### Memory NK cells in viral infection

The MCMV model initially established by the Lanier laboratory has traditionally been used for memory NK cell research.<sup>16,34</sup> As in T



**Fig. 1** Generation and maintenance of memory ILCs. ILCs, including NK cells, ILC1s, and ILC2s, are reported to exhibit adaptive features. Ly49H<sup>+</sup> NK cells directly recognize the MCMV-m157 protein and are completely activated with the help of costimulatory and proinflammatory cytokine signals. The transcription factors Zbtb32, STAT4, Runx1/3, and CBF-β are critical for Ly49H<sup>+</sup> NK cell expansion. Ly49H<sup>+</sup> NK cells subsequently undergo a contraction phase. A small population of these cells survive against apoptosis in an autophagy-dependent manner and switch to a memory state via an epigenetic program. IL-15 is required for memory Ly49H<sup>+</sup> NK-cell longevity. Cytokines can induce non-specific memory potential in NK cells. Activation signals from combinations of cytokines induce the generation of long-lasting epigenetic imprinting of the *Irfng* locus. Both CD49a<sup>+</sup> liver-resident NK cells and CD49b<sup>+</sup> cNK cells have been reported to be responsible for hapten-induced immunological memory. CD49b<sup>+</sup> cNK cells express Ly49C/I, which may interact with Ly49C/I-sensitive self-peptide-hapten complexes. CD49a<sup>+</sup> liver-resident NK cells contain an IL-7Rα<sup>+</sup> subset that conforms to the definition of ILC1s. IL-7Rα<sup>+</sup> ILC1s, reported to highly express CXCR6 and CXCR3, acquire memory in draining LNs and maintain long-term survival in the liver. Notably, whether CD49a<sup>+</sup> liver-resident NK cells respond locally to haptens and viruses (influenza virus, VSV, and HIV) has not been determined. Lung ST2<sup>+</sup> ILC2s acquire memory upon IL-33 stimulation. Memory ILC2s exhibit a greater production of IL-5 and IL-13 in recall responses. cNK cells, conventional NK cells; HIV, human immunodeficiency virus type 1; ILCs, innate lymphoid cells; LN, lymph node; MCMV, mouse cytomegalovirus; NK cells, natural killer cells; VSV, vesicular stomatitis virus

cells, three signals are required for MCMV-specific NK cell clonal expansion (Fig. 1). Binding of the activating Ly49H receptor to the viral m157 protein is the first signal and leads to the activation of the adaptor protein DAP12.<sup>16</sup> In addition to Ly49H, the activating receptor Ly49D either directly drives NK cell memory formation against the H-2D<sup>d</sup> MHC class I alloantigen in the setting of allogeneic bone marrow transplantation<sup>35</sup> or enhances memory differentiation of Ly49H<sup>+</sup> NK cells in the setting of MCMV infection.<sup>36</sup> Binding of the co-stimulatory receptor CD226 to CD155 and CD112 is the second signal.<sup>37</sup> The third signal involves pro-inflammatory cytokines, including IL-12, IFN- $\alpha/\beta$ , IL-18, and IL-33.<sup>38–41</sup> IL-12 drives the expression of STAT4 and Zbtb32,<sup>38,42</sup> while IFN- $\alpha$  is required for the expression of STAT1, STAT2, and IRF9.<sup>43</sup> Zbtb32<sup>-/-</sup> NK cells exhibit decreased antiviral activity and impaired memory Ly49H<sup>+</sup> NK cell generation.<sup>42</sup> Zbtb32 allows NK cell activation and proliferation via the suppression of Blimp-1. STAT4 binds to the promoter regions of *Runx1* and *Runx3* genes, promoting the expression of Runx1 and Runx3 transcription factors.<sup>44</sup> Runx1 is responsible for controlling the cell cycle in Ly49H<sup>+</sup> NK cells. Ly49H<sup>+</sup> NK cell expansion and survival were found to be impaired in STAT1-, STAT2-, and IRF9- deficient mice, underscoring a non-redundant role for IFN- $\alpha/\beta$  signaling in memory Ly49H<sup>+</sup> NK cell generation.<sup>43</sup> One week after MCMV infection, Ly49H<sup>+</sup> NK cells were found to expand to the peak number—up to a 10-fold increase in B6 mice or a 1000-fold increase in a transfer model.<sup>16</sup> Ly49H<sup>+</sup> NK cells subsequently enter a contraction stage as the pro-apoptotic molecule Bim mediates the dramatic loss of effector Ly49H<sup>+</sup> NK cells.<sup>45</sup> A small effector Ly49H<sup>+</sup> NK cell population survives in an autophagy-dependent manner during transition to the memory pool.<sup>46</sup> The process of autophagy helps to clear damaged mitochondria and reduce reactive oxygen species levels, thus protecting the effector Ly49H<sup>+</sup> NK cells with memory potential from undergoing apoptosis. Ly49H<sup>+</sup> NK cells deficient in the mitochondria-associated protein BNIP3 or BNIP3L exhibit impaired memory-pool generation.<sup>46</sup> Maturely differentiated memory Ly49H<sup>+</sup> NK cells exhibit the Ly6C<sup>+</sup>KLRG1<sup>+</sup> phenotype.<sup>47,48</sup> However, the mechanism by which effector Ly49H<sup>+</sup> NK cells switch to a memory state is yet to be detailed. A previous study showed continuous transcriptome changes in Ly49H<sup>+</sup> NK cells during their differentiation from naive to effector and memory states.<sup>47</sup> Sun and colleagues recently clarified the sequential transition of naive, effector, and memory Ly49H<sup>+</sup> NK cells in terms of epigenetic regulation.<sup>49</sup> The cytotoxicity and interferon-stimulated response element pathways were associated with increased chromatin accessibility in memory-state Ly49H<sup>+</sup> NK cells, while chromatin regions associated with TCF-LEF transcription factors and nuclear factor- $\kappa$ B family members were found to have decreased accessibility.<sup>49</sup> Chromatin architecture dynamics provide insight to the precise regulatory mechanisms responsible for the switching of NK cells between effector and memory states.

Memory Ly49H<sup>+</sup> NK cells exhibit features in common with CD8<sup>+</sup> T cells.<sup>50</sup> The dynamics, molecular regulation, transcriptome, and epigenetic program of MCMV-specific memory NK cells are comparable to those of CD8<sup>+</sup> T cells.<sup>16,34,47,49</sup> Both Ly49H<sup>+</sup> NK and MCMV-specific CD8<sup>+</sup> T cells undergo expansion (days 0–7), contraction (days 7–14/28), and stable memory (days > 28) phases.<sup>16</sup> Three signals, which involve recognition receptors, co-stimulatory molecules, and pro-inflammatory cytokines, are required for the complete activation of Ly49H<sup>+</sup> NK and CD8<sup>+</sup> T cells. These two cell types share the same regulators of memory generation and maintenance, including IL-15, Bim, autophagy, and epigenetic programs. However, effector and memory T cells use different metabolic pathways. Effector T cells exhibit elevated aerobic glycolysis and preferentially metabolize glucose.<sup>51,52</sup> Metabolic switching from glycolysis to intrinsic fatty acid oxidation is critical for the generation and long-term survival of memory T cells.<sup>53,54</sup> Recent studies have reported that metabolic reprogramming contributes to NK cell dysfunction,

demonstrating how critical metabolic regulation is for NK cell function and survival.<sup>55</sup> Adaptive NKG2C<sup>+</sup> NK cells from HCMV-seropositive individuals exhibit increased glycolysis and mitochondrial oxidative metabolism, similar to T cells.<sup>56</sup> AT-rich interaction domain 5B is essential for the generation of mitochondrial membrane potential, oxidative metabolism, the production of IFN- $\gamma$ , and the survival of adaptive NK cells.<sup>56</sup>

NK cell deficiency often results in an increased risk of lethal HCMV infection,<sup>57</sup> underscoring the critical role that NK cells play in controlling this virus. NKG2C<sup>+</sup> NK cell populations have been reported to undergo expansion and activation via NKG2C signaling in HCMV-seropositive individuals.<sup>19</sup> HCMV reactivation induces the preferential expansion of NKG2C<sup>+</sup> NK cells, and these expanded cells can survive for at least 1 year.<sup>19</sup> Similarly, long-lasting memory-like NK cells have been reported in hantavirus<sup>58</sup> and hepatitis patients.<sup>59</sup> Notably, NKG2C<sup>+</sup> NK cell expansion has been observed only in patients concomitantly infected with HCMV, implying that HCMV indeed drives human memory-like NK cell generation. Consistent with these findings, a recent study identified memory NKG2C<sup>+</sup> NK cells using RNA-based flow cytometry in rhesus macaques infected with CMV and SIV.<sup>60</sup> The receptors platelet-derived growth factor- $\alpha$  receptor and neuropilin-2 facilitate the entry of HCMV into epithelial and endothelial cells.<sup>61</sup> HLA-E on infected cells presents HCMV-encoded UL40 peptides to NKG2C/CD94 complexes on human NK cells.<sup>62</sup> A single amino-acid substitution in UL40 was found to result in failed human NKG2C<sup>+</sup> NK cell responses.<sup>62</sup> NKG2C–UL40 interaction thus serves as the first signal to activate HCMV-specific NK cells. Whether the second signal mediated by co-stimulatory molecules is required has not yet been determined. Monocyte-derived IL-12 serves as the third signal for human NKG2C<sup>+</sup> NK-cell activation.<sup>63</sup> Among human NKG2C<sup>+</sup> NK cells, Fc $\gamma$ R<sup>+</sup> populations exhibit the most robust responses against HCMV and influenza virus in an antibody-dependent manner.<sup>64,65</sup> CMV-driven adaptive Fc $\gamma$ R<sup>+</sup> NK cells are present throughout the body and preferentially migrate to mucosal sites.<sup>66</sup> CMV infection activates the atypical CD3 $\zeta$ –Zap70 signaling pathway instead of the  $\gamma$ -chain–Syk pathway in Fc $\gamma$ R<sup>+</sup> NK cells.<sup>66</sup> In Fc $\gamma$ R<sup>+</sup> NK cells, DNA methylation associated with the tyrosine kinase SYK deficiency occurs in the promoter region of the genes encoding PLZF, HELIOS, DAB2, and EAT-2, implying that epigenetic modifications are critical for HCMV-induced memory-like NK-cell development.<sup>65</sup> Furthermore, the conserved noncoding sequence at the *IFNG* locus exhibits high accessibility in long-lasting NKG2C<sup>+</sup> NK cells.<sup>67</sup> Upon secondary stimulation, these epigenetic modifications allow a faster production of IFN- $\gamma$  by human memory NK cells.

Memory NK cells are widely present in both mice and primates infected with viruses. Paust et al. reported that liver NK cells recall sensitization to influenza virus, human immunodeficiency virus type 1, and vesicular stomatitis virus, protecting mice from lethal secondary infections.<sup>22</sup> Liver CXCR6<sup>+</sup> NK cells may play a key role in the defense against viral challenges in vaccinated mice. Notably, influenza virus-induced memory NK cells were found to be concentrated among populations of liver CD49a<sup>+</sup> NK cells that highly expressed CXCR6.<sup>68</sup> Moreover, NK cells from macaques infected with SIV were reported to specifically lyse Gag- and Env-pulsed dendritic cells, demonstrating the presence of memory NK cells in primates.<sup>18</sup> As in the setting of HCMV infection, NKG2C participates in SIV-induced memory NK-cell generation.<sup>18,60</sup> A study found that CD56<sup>dim</sup> NK cells from healthy individuals vaccinated against influenza virus exhibit a higher production of IFN- $\gamma$  upon restimulation by influenza virus and that NKp46 internalization represents the memory state of human NK cells.<sup>69</sup> Importantly, these aforementioned studies provide insight for novel NK cell-based vaccine-development strategies.

#### Cytokine-induced memory NK cells

The Yokoyama laboratory first established a memory NK cell model in the absence of specific antigens.<sup>17</sup> Cytokines IL-12, -15,

and -18 have been found to induce the memory potential of cNK cells. NK cells pre-activated by cytokine combinations and transferred into naive mice exhibit a stronger IFN- $\gamma$  production than naive NK cells upon secondary stimulation with IL-12, IL-15, or other activating receptors.<sup>17</sup> Due to the lack of specific antigen recognition, this form of memory NK cells has been termed non-specific memory NK cells (Fig. 1). Cytokine-induced memory NK cells last for at least 12 weeks, emphasizing their longevity.<sup>70</sup> A follow-up study found that the memory potential of cytokine-induced NK cells can be transferred to their daughter cells not previously exposed to those cytokines, implying that NK cells acquire memory in an intrinsic manner and that an epigenetic-dependent mechanism may promote memory formation.<sup>70</sup> Consistent with these results, another study reported that cytokine stimulation results in the demethylation of genes encoding IFN- $\gamma$ , implying that a long-lasting epigenetic imprinting of the *Irfg* locus is responsible for recall responses of memory NK cells and their daughter cells.<sup>71</sup> Tissue-resident NK cells are present in multiple tissues and show developmental and functional features distinct from those of cNK cells.<sup>26</sup> It would be of great interest to determine whether tissue-resident NK cells exhibit memory characteristics upon stimulation with cytokines or other antigens, similar to tissue-resident memory T cells. Tissue-resident memory NK cells may confer early immunoprotection at barrier sites.

In addition, cytokines induce the memory characteristics of human NK cells. Similar to murine memory NK cells, human CD56<sup>bright</sup> and CD56<sup>dim</sup> NK cells preactivated by IL-12, -15, and -18 were reported to exhibit increased production of IFN- $\gamma$  upon secondary stimulation with IL-12 + IL-15, IL-12 + IL-18, or K562 leukemia cells.<sup>72</sup> Cytokine-induced human memory NK cells can persist for at least 3 weeks.<sup>72</sup> CD94<sup>+</sup>NKG2A<sup>+</sup>NKG2C<sup>+</sup>CD69<sup>+</sup>CD57<sup>-</sup>KIR<sup>-</sup> NK cells may be responsible for the memory formation potential.<sup>72</sup> Like murine NK cells, daughter cells of cytokine-activated human NK cells exhibit recall capacity.<sup>72</sup> Surprisingly, NK cells stimulated with CD16, IL-12, IL-18, or other activating signals also exhibit enhanced IFN- $\gamma$  production upon restimulation.<sup>72</sup> Unique patterns of activating signals seem to be required for human memory NK cell generation. These memory NK cells may exist under a variety of physiological conditions. During pregnancy, uterine-resident NK cells can proliferate<sup>73</sup> and secrete growth factors, promoting fetal development.<sup>74</sup> A recent study reported that human NKG2C<sup>+</sup> NK cells expand in repeated pregnancies, and these cells were termed pregnancy-trained decidual NK cells (PTdNKs).<sup>75</sup> Like cytokine-induced memory NK cells, PTdNKs possess easily accessible chromatin at the *IFNG* locus.<sup>75</sup> HLA-E, HLA-G, and IL-15 may play vital roles in the generation of memory-like PTdNKs.<sup>75</sup>

Several studies have highlighted the applications of cytokine-induced memory NK cells in tumor immunotherapy. Memory NK cells have the advantages of robust recall responses, longevity, and non-specific features to control tumor development. A single injection of murine NK cells pre-activated with IL-12/IL-15/IL-18, in combination with irradiation therapy, efficiently reduced RMA-S lymphoma growth.<sup>76</sup> Memory NK cells exhibit increased IL-2R $\alpha$  expression, suggesting that IL-2 may allow pre-activated donor NK cells to rapidly proliferate and accumulate in cancerous tissue.<sup>76</sup> In a first-in-human phase 1 clinical trial (NCT01898793), human memory NK cells were successfully used to induce complete remission in four of the nine acute myeloid leukemia patients.<sup>77</sup> These findings demonstrate that memory NK cells hold great promise in the development of novel antitumor immunotherapies.

### MEMORY ILC1S

ILC1s are defined as non-cytotoxic IFN- $\gamma$ /TNF-producing helper innate lymphoid cells.<sup>1-6</sup> ILC1s function as the first line of immune defense against viruses, acting earlier even than cNK cells.<sup>7</sup> A recent study, however, detailed the memory features of ILC1s,

reporting that these cells mediate hapten-induced long-term recall responses.<sup>20</sup> Unique thymic IL-7R $\alpha$ <sup>+</sup> NK cells were described in 2006.<sup>78</sup> Thymic NK cells represent a lineage different from bone marrow (BM)-derived NK cells. A follow-up study found that LNs also contain IL-7R $\alpha$ <sup>+</sup> NK cells that develop via thymus-dependent and thymus-independent pathways.<sup>79</sup> Thymic and LN IL-7R $\alpha$ <sup>+</sup> NK cells are currently classified as ILC1s.<sup>1,80</sup> Interestingly, hapten sensitization induces the increased recruitment of IL-7R $\alpha$ <sup>+</sup> ILC1s into skin-draining LNs in a CXCR3-dependent manner<sup>20</sup> (Fig. 1). IL-7R $\alpha$ <sup>+</sup> ILC1s express CXCR6 and CD49a, while IL-7R $\alpha$ <sup>-</sup> cNK cells do not. ILC1s are activated by haptens and subsequently acquire hapten-specific memory potential in draining LNs.<sup>20</sup> Although IL-7R $\alpha$ <sup>+</sup> ILC2s and ILC3s have been shown to reside within interfollicular spaces in LNs,<sup>81</sup> the location of naive and hapten-sensitized IL-7R $\alpha$ <sup>+</sup> ILC1s has not yet been determined. After egress from LNs, memory IL-7R $\alpha$ <sup>+</sup> ILC1s selectively reside in the liver via CXCR6-CXCL16 interaction.<sup>20</sup> The cytokine IL-7 is critical for the longevity of LN-derived memory ILC1s.<sup>20</sup> As IL-7R $\alpha$  deficiency does not affect the levels of the anti-apoptotic protein BCL-2 in ILC1s,<sup>82</sup> a BCL-2-independent mechanism may be required for the longevity of ILC1 memory. The liver, rich in CXCL16<sup>83,84</sup> and IL-7,<sup>85,86</sup> serves as a suitable niche for the residency and long-term maintenance of LN-derived memory IL-7R $\alpha$ <sup>+</sup> ILC1s. Thus, the LN-liver axis is critical for memory IL-7R $\alpha$ <sup>+</sup> ILC1 generation and maintenance. Although liver IL-7R $\alpha$ <sup>+</sup> ILC1s from LN-deficient mice cannot mediate a vigorous CHS response, the possibility that the local response of these cells to haptens requires intact LNs has not been excluded. Whether liver- and LN-derived memory IL-7R $\alpha$ <sup>+</sup> ILC1s can act in a non-mutually exclusive way thus remains to be investigated.

ACD is a major cause of occupational skin disease, accounting for 20% of all work-related health complaints.<sup>87</sup> IFN- $\gamma$ - and TNF-producing CD3<sup>+</sup>CD56<sup>bright</sup> NK cells accumulate in the inflamed skin of ACD patients.<sup>88</sup> These NK cells express CXCR3,<sup>88</sup> a chemokine reported to be critical for murine memory ILC1 generation,<sup>20</sup> suggesting that human CD56<sup>bright</sup> NK cells or ILC1s may be involved in memory responses. However, human NK cells from ACD patients were not found to exhibit recall responses to nickel,<sup>88</sup> suggesting that human NK cells cannot directly recognize allergens. A humanized mouse model may be suitable for further studies of the memory features of human NK cells and other ILCs in vivo.

Memory ILC1s are both similar to and different from memory T cells. Despite their different homing sites, both memory ILC1s and central memory T cells (T<sub>CM</sub>) have unique migratory patterns. After the generation of memory cells in secondary lymphoid tissues, T<sub>CM</sub> cells preferentially home to BM,<sup>89</sup> while memory ILC1s selectively reside in the liver for long-term survival.<sup>20</sup> Although the primary site of hematopoiesis transitions from the fetal liver to the BM during ontogeny, the adult liver retains partial hematopoietic potential,<sup>90,91</sup> possibly supporting the longevity of memory ILC1s. IL-7 has been found to be essential for the longevity of both memory ILC1s<sup>20</sup> and T cells.<sup>92-94</sup> Whether memory ILC1s, like memory T cells, take advantage of IL-7-mediated fatty acid oxidation metabolism to survive warrants investigation. The role of IL-15, another factor critical to memory T<sup>95-97</sup> and NK<sup>98</sup> cells, has not been determined in memory ILC1 development. ILC1s acquire memory potential at day 3, before T cells differentiate into memory cells, underscoring a difference in the memory dynamics between ILC1s and T cells. Despite such advances, the mechanisms of hapten recognition by ILC1s and the regulation of memory ILC1 generation in LNs are yet to be precisely detailed.

### MEMORY ILC2S

ILC2s are traditionally defined as IL-4-, IL-5-, and IL-13-producing, ROR $\alpha$ - and GATA3-dependent ILC subsets that mediate type 2 responses in the early stage of allergen-induced inflammation and

**Table 1.** Characteristics of memory ILC subsets

	Phenotype	Location	Antigen/cytokine	Recall responses	Specificity	Longevity	References
<b>NK cells</b>	NKp46 <sup>+</sup> CD49b <sup>+</sup> Ly49H <sup>+</sup>	Spleen, liver	MCMV-m157	+	+	+	16,34–50
	NKp46 <sup>+</sup> CD49b <sup>+</sup>	Spleen	IL-12/15/18	+	-	+	17
	NKp46 <sup>+</sup> CD49b <sup>+</sup> Ly49C/I <sup>+</sup>	Liver	Haptens	+	+	+	15,32,33
<b>ILC1s</b>	NKp46 <sup>+</sup> CD49a <sup>+</sup> CXCR6 <sup>+</sup> IL-7R $\alpha$ <sup>+</sup>	LN, liver	Haptens	+	+	+	15,20,22,23
<b>ILC2s</b>	Lin <sup>-</sup> ST2 <sup>+</sup> Thy-1 <sup>+</sup> KLRG1 <sup>+</sup>	LN, lung	IL-33	+	-	+	21
<b>ILC3s</b>	ND	ND	ND	ND	ND	ND	

ILC innate lymphoid cell, LN lymph node, MCMV mouse cytomegalovirus. “+,” positive; “-,” negative; ND, not determined

parasitic infection.<sup>1–4,8,9</sup> Memory-like features of ILC2s have recently been revealed<sup>21</sup> (Fig. 1), and advances in the understanding of memory ILC2s have been well reviewed in the studies of Martinez-Gonzalez and colleagues.<sup>99,100</sup> IL-33 and allergens induce the rapid expansion and contraction of ILC2 populations. ILC2s seem unable to directly recognize allergens and are activated by epithelial cell-derived IL-33, IL-25, and thymic stromal lymphopoietin (TSLP). Interestingly, memory ILC2s in the lung produce higher levels of IL-5 and IL-13 in recall responses.<sup>21</sup> Compared to naive ILC2s, memory ILC2s initiate adaptive responses of Th2 cells with a greater efficiency. Like those of cytokine-induced memory NK cells, ILC2-mediated memory responses are non-specific.<sup>21</sup> Naive lung ILC2s express low levels of IL-25R, while memory ILC2s exhibit sustained increases in IL-25R expression.<sup>21</sup> Another study showed that CD25<sup>-</sup> and CD25<sup>+</sup> ILC2s respond to initial allergen sensitization with different dynamics.<sup>101</sup> CD25<sup>-</sup> subsets are short-lived, while CD25<sup>+</sup> subsets exhibit long-term survival.<sup>101</sup> Thus, IL-25R and CD25 may serve as reliable markers for distinguishing lung memory ILC2s from naive ILC2s. Since IL-33 and allergens also induce the expansion of LN ILC2s,<sup>21</sup> it is of great relevance to explore whether LN ILC2s possess memory potential and the ways in which LN and lung ILC2 memory are associated. Considering that the LN–liver axis has been revealed to be critical for memory ILC1 generation and maintenance,<sup>20</sup> a similar migratory pattern of memory ILC2s may exist. Although the mechanism underlying the generation and maintenance of ILC2s remains largely unknown, the discovery of memory ILC2s illuminates the role of innate immune cells in chronic allergic inflammation.

### CONCLUDING REMARKS

Although the development and innate functions of ILCs have been well documented, the study of the adaptive features of ILCs is newly emerging. Over the past decade, evidence supporting ILC memory, in particular NK cell memory induced by haptens, CMV, and cytokines, ILC1 memory induced by haptens, and ILC2 memory induced by allergens, has accumulated (Table 1). Although memory ILC1s and ILC2s have not been reported in humans, memory NK cells have been found in patients suffering from viral infections and play a critical role in host defense. Recent findings bring ILCs into the adaptive immunity arena. The emergence of ILC memory helps to revise the traditionally understood progression of inflammation, viral infection, and tumor development. Importantly, circulating and tissue-resident memory ILCs may provide earlier protection from pathogens at barrier tissues. Based on the immunological memory features of ILCs, new vaccination and tumor immunotherapy strategies are emerging; for example, the use of cytokine-induced memory NK cells for curing cancer patients. Thus, the accumulating knowledge about ILC memory greatly expands the ILC field in terms of basic research and applications.

In the study of ILC memory, several major questions remain to be answered: (i) whether ILC3s and LT $\alpha$ i cells possess memory properties;

(ii) how memory NK cells and ILC1s recognize specific antigens, including different viruses and haptens, as they lack diverse receptors; (iii) to what extent, memory ILCs exhibit features common to memory T cells; (iv) how to effectively establish humanized mice models and in vitro recall systems to confirm the presence of human memory ILCs; and (v) how to efficiently apply ILC memory to improve vaccines and tumor immunotherapies. Along with a further understanding of basic ILC memory biology, increased therapeutic application of memory ILCs in human diseases will be actualized.

### ACKNOWLEDGEMENTS

This work was supported by the Natural Science Foundation of China (#81788101, 81761128013, 81571522, 91642105, 91542114, and 91542000).

### ADDITIONAL INFORMATION

**Competing interests:** The authors declare no competing interests.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

### REFERENCES

- Spits, H. et al. Innate lymphoid cells—a proposal for uniform nomenclature. *Nat. Rev. Immunol.* **13**, 145–149 (2013).
- Eberl, G., Colonna, M., Di Santo, J. P. & McKenzie, A. N. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology. *Science* **348**, aaa6566 (2015).
- Artis, D. & Spits, H. The biology of innate lymphoid cells. *Nature* **517**, 293–301 (2015).
- Vivier, E. et al. Innate lymphoid cells: 10 years on. *Cell* **174**, 1054–1066 (2018).
- Fuchs, A. et al. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN- $\gamma$ -producing cells. *Immunity* **38**, 769–781 (2013).
- Klose, C. S. N. et al. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* **157**, 340–356 (2014).
- Weizman, O. E. et al. ILC1 confer early host protection at initial sites of viral infection. *Cell* **171**, 795–808 (2017). e712.
- Moro, K. et al. Innate production of TH2 cytokines by adipose tissue-associated c-Kit+Sca-1+ lymphoid cells. *Nature* **463**, 540 (2009).
- Neill, D. R. et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* **464**, 1367 (2010).
- Cella, M. et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* **457**, 722 (2008).
- Cupedo, T. et al. Human fetal lymphoid tissue-inducer cells are interleukin 17-producing precursors to ROR $\gamma$ CD127+natural killer-like cells. *Nat. Immunol.* **10**, 66 (2008).
- Luci, C. et al. Influence of the transcription factor ROR $\gamma$ t on the development of NKp46+ cell populations in gut and skin. *Nat. Immunol.* **10**, 75 (2008).
- Satoh-Takayama, N. et al. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. *Immunity* **29**, 958–970 (2008).
- Mebius, R. E., Rennert, P. & Weissman, I. L. Developing lymph nodes collect CD4+CD3–LT $\beta$ + cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. *Immunity* **7**, 493–504 (1997).

15. O'Leary, J. G., Goodarzi, M., Drayton, D. L. & von Andrian, U. H. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. *Nat. Immunol.* **7**, 507–516 (2006).
16. Sun, J. C., Beilke, J. N. & Lanier, L. L. Adaptive immune features of natural killer cells. *Nature* **457**, 557–561 (2009).
17. Cooper, M. A. et al. Cytokine-induced memory-like natural killer cells. *Proc. Natl. Acad. Sci. USA* **106**, 1915–1919 (2009).
18. Reeves, R. K. et al. Antigen-specific NK cell memory in rhesus macaques. *Nat. Immunol.* **16**, 927–932 (2015).
19. Lopez-Verges, S. et al. Expansion of a unique CD57(+)NKG2Chi natural killer cell subset during acute human cytomegalovirus infection. *Proc. Natl. Acad. Sci. USA* **108**, 14725–14732 (2011).
20. Wang, X. et al. Memory formation and long-term maintenance of IL-7Ralpha(+) ILC1s via a lymph node-liver axis. *Nat. Commun.* **9**, 4854 (2018).
21. Martinez-Gonzalez, I. et al. Allergen-experienced group 2 innate lymphoid cells acquire memory-like properties and enhance allergic lung inflammation. *Immunity* **45**, 198–208 (2016).
22. Paust, S. et al. Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. *Nat. Immunol.* **11**, 1127–1135 (2010).
23. Peng, H. et al. Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. *J. Clin. Invest.* **123**, 1444–1456 (2013).
24. Peng, H., Sun, R. & Liver-resident, N. K. cells and their potential functions. *Cell. Mol. Immunol.* **14**, 890 (2017).
25. Peng, H., Wisse, E. & Tian, Z. Liver natural killer cells: subsets and roles in liver immunity. *Cell. Mol. Immunol.* **13**, 328–336 (2016).
26. Sojka, D. K. et al. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *eLife* **3**, e01659 (2014).
27. Fan, X. & Rudensky, A. Y. Hallmarks of tissue-resident lymphocytes. *Cell* **164**, 1198–1211 (2016).
28. Tang, L. et al. Differential phenotypic and functional properties of liver-resident NK cells and mucosal ILC1s. *J. Autoimmun.* **67**, 29–35 (2016).
29. Yu, Y. et al. Single-cell RNA-seq identifies a PD-1hi ILC progenitor and defines its development pathway. *Nature* **539**, 102–106 (2016).
30. Constantinides, M. G., McDonald, B. D., Verhoef, P. A. & Bendelac, A. A committed precursor to innate lymphoid cells. *Nature* **508**, 397 (2014).
31. Zhang, L. H., Shin, J. H., Haggadone, M. D. & Sunwoo, J. B. The aryl hydrocarbon receptor is required for the maintenance of liver-resident natural killer cells. *J. Exp. Med.* **213**, 2249–2257 (2016).
32. van den Boorn, J. G. et al. Inflammasome-dependent induction of adaptive NK cell memory. *Immunity* **44**, 1406–1421 (2016).
33. Wight, A. et al. Critical role for the Ly49 family of class I MHC receptors in adaptive natural killer cell responses. *Proc. Natl. Acad. Sci. USA* **115**, 11579–11584 (2018).
34. O'Sullivan, T. E., Sun, J. C. & Lanier, L. L. Natural killer cell memory. *Immunity* **43**, 634–645 (2015).
35. Nabekura, T. & Lanier, L. L. Antigen-specific expansion and differentiation of natural killer cells by alloantigen stimulation. *J. Exp. Med.* **211**, 2455–2465 (2014).
36. Nabekura, T. & Lanier, L. L. Activating receptors for self-MHC class I enhance effector functions and memory differentiation of NK cells during mouse cytomegalovirus infection. *Immunity* **45**, 74–82 (2016).
37. Nabekura, T. et al. Costimulatory molecule DNAM-1 is essential for optimal differentiation of memory natural killer cells during mouse cytomegalovirus infection. *Immunity* **40**, 225–234 (2014).
38. Sun, J. C. et al. Proinflammatory cytokine signaling required for the generation of natural killer cell memory. *J. Exp. Med.* **209**, 947–954 (2012).
39. Madera, S. et al. Type I IFN promotes NK cell expansion during viral infection by protecting NK cells against fratricide. *J. Exp. Med.* **213**, 225–233 (2016).
40. Madera, S. & Sun, J. C. Cutting edge: stage-specific requirement of IL-18 for antiviral NK cell expansion. *J. Immunol.* **194**, 1408–1412 (2015).
41. Nabekura, T., Girard, J. P. & Lanier, L. L. IL-33 receptor ST2 amplifies the expansion of NK cells and enhances host defense during mouse cytomegalovirus infection. *J. Immunol.* **194**, 5948–5952 (2015).
42. Beaulieu, A. M., Zawislak, C. L., Nakayama, T. & Sun, J. C. The transcription factor Zbtb32 controls the proliferative burst of virus-specific natural killer cells responding to infection. *Nat. Immunol.* **15**, 546–553 (2014).
43. Geary, C. D. et al. Non-redundant ISGF3 components promote NK cell survival in an auto-regulatory manner during viral infection. *Cell Rep.* **24**, 1949–1957 (2018). e1946.
44. Rapp, M. et al. Core-binding factor  $\beta$  and Runx transcription factors promote adaptive natural killer cell responses. *Sci. Immunol.* **2**, pii: ean379 (2017).
45. min-Oo, G., Bezman, N. A., Madera, S., Sun, J. C. & Lanier, L. L. Proapoptotic Bim regulates antigen-specific NK cell contraction and the generation of the memory NK cell pool after cytomegalovirus infection. *J. Exp. Med.* **211**, 1289–1296 (2014).
46. O'Sullivan, T. E., Johnson, L. R., Kang, H. H. & Sun, J. C. BNP3- and BNP3L-mediated mitophagy promotes the generation of natural killer cell memory. *Immunity* **43**, 331–342 (2015).
47. Bezman, N. A. et al. Molecular definition of the identity and activation of natural killer cells. *Nat. Immunol.* **13**, 1000–1009 (2012).
48. min-Oo, G. & Lanier, L. L. Cytomegalovirus generates long-lived antigen-specific NK cells with diminished bystander activation to heterologous infection. *J. Exp. Med.* **211**, 2669–2680 (2014).
49. Lau, C. M. et al. Epigenetic control of innate and adaptive immune memory. *Nat. Immunol.* **19**, 963–972 (2018).
50. Rapp, M., Wiedemann, G. M. & Sun, J. C. Memory responses of innate lymphocytes and parallels with T cells. *Semin. Immunopathol.* **40**, 343–355 (2018).
51. Buck, M. D., O'Sullivan, D. & Pearce, E. L. T cell metabolism drives immunity. *J. Exp. Med.* **212**, 1345–1360 (2015).
52. Bantug, G. R., Galluzzi, L., Kroemer, G. & Hess, C. The spectrum of T cell metabolism in health and disease. *Nat. Rev. Immunol.* **18**, 19–34 (2018).
53. Pearce, E. L. et al. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature* **460**, 103–107 (2009).
54. Cui, G. et al. IL-7-induced glycerol transport and TAG synthesis promotes memory CD8+ T cell longevity. *Cell* **161**, 750–761 (2015).
55. Cong, J. et al. Dysfunction of natural killer cells by FBP1-induced inhibition of glycolysis during lung cancer progression. *Cell. Metab.* **28**, 243–255 (2018). e245.
56. Cichocki, F. et al. ARID5B regulates metabolic programming in human adaptive NK cells. *J. Exp. Med.* **215**, 2379–2395 (2018).
57. Orange, J. S. Natural killer cell deficiency. *J. Allergy Clin. Immunol.* **132**, 515–526 (2013).
58. Bjorkstrom, N. K. et al. Rapid expansion and long-term persistence of elevated NK cell numbers in humans infected with hantavirus. *J. Exp. Med.* **208**, 13–21 (2011).
59. Beziat, V. et al. CMV drives clonal expansion of NKG2C+ NK cells expressing self-specific KIRs in chronic hepatitis patients. *Eur. J. Immunol.* **42**, 447–457 (2012).
60. Ram, D. R. et al. Tracking KLR2C(NKG2C)+memory-like NK cells in SIV+and rhCMV+rhesus macaques. *PLoS. Pathog.* **14**, e1007104 (2018).
61. Martinez-Martin, N. et al. An unbiased screen for human cytomegalovirus identifies neuropilin-2 as a central viral receptor. *Cell* **174**, 1158–1171 (2018). e1119.
62. Hammer, Q. et al. Peptide-specific recognition of human cytomegalovirus strains controls adaptive natural killer cells. *Nat. Immunol.* **19**, 453–463 (2018).
63. Rolle, A. et al. IL-12-producing monocytes and HLA-E control HCMV-driven NKG2C+ NK cell expansion. *J. Clin. Invest.* **124**, 5305–5316 (2014).
64. Zhang, T., Scott, J. M., Hwang, I. & Kim, S. Cutting edge: antibody-dependent memory-like NK cells distinguished by FcRgamma deficiency. *J. Immunol.* **190**, 1402–1406 (2013).
65. Lee, J. et al. Epigenetic modification and antibody-dependent expansion of memory-like NK cells in human cytomegalovirus-infected individuals. *Immunity* **42**, 431–442 (2015).
66. Shah, S. V. et al. CMV primes functional alternative signaling in adaptive  $\Delta$ g NK cells but is subverted by lentivirus infection in rhesus macaques. *Cell Rep.* **25**, 2766–2774 (2018). e2763.
67. Luetke-Eversloh, M. et al. Human cytomegalovirus drives epigenetic imprinting of the IFNG locus in NKG2Chi natural killer cells. *PLoS. Pathog.* **10**, e1004441 (2014).
68. Li, T. et al. Respiratory influenza virus infection induces memory-like liver NK cells in mice. *J. Immunol.* **198**, 1242–1252 (2017).
69. Dou, Y. et al. Influenza vaccine induces intracellular immune memory of human NK cells. *PLoS. One.* **10**, e0121258 (2015).
70. Keppel, M. P., Yang, L. & Cooper, M. A. Murine NK cell intrinsic cytokine-induced memory-like responses are maintained following homeostatic proliferation. *J. Immunol.* **190**, 4754–4762 (2013).
71. Ni, J. et al. Adoptively transferred natural killer cells maintain long-term anti-tumor activity by epigenetic imprinting and CD4(+) T cell help. *Oncot Immunology* **5**, e1219009 (2016).
72. Romee, R. et al. Cytokine activation induces human memory-like NK cells. *Blood* **120**, 4751–4760 (2012).
73. Sojka, D. K., et al. Cutting edge: local proliferation of uterine tissue-resident NK cells during decidualization in mice. *J. Immunol.* **201**, 2551–2556 (2018).
74. Fu, B. et al. Natural killer cells promote fetal development through the secretion of growth-promoting factors. *Immunity* **47**, 1100–1113 (2017). e1106.
75. Gamliel, M. et al. Trained memory of human uterine NK cells enhances their function in subsequent pregnancies. *Immunity* **48**, 951–962 (2018). e955.
76. Ni, J., Miller, M., Stojanovic, A., Garbi, N. & Cerwenka, A. Sustained effector function of IL-12/15/18-primed NK cells against established tumors. *J. Exp. Med.* **209**, 2351–2365 (2012).

77. Romee, R. et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci. Transl. Med.* **8**, 357ra123–357ra123 (2016).
78. Vosshenrich, C. A. et al. A thymic pathway of mouse natural killer cell development characterized by expression of GATA-3 and CD127. *Nat. Immunol.* **7**, 1217–1224 (2006).
79. Luther, C., Warner, K. & Takei, F. Unique progenitors in mouse lymph node develop into CD127+NK cells: thymus-dependent and thymus-independent pathways. *Blood* **117**, 4012–4021 (2011).
80. Spits, H. & Di Santo, J. P. The expanding family of innate lymphoid cells: regulators and effectors of immunity and tissue remodeling. *Nat. Immunol.* **12**, 21–27 (2011).
81. Mackley, E. C. et al. CCR7-dependent trafficking of RORgamma(+) ILCs creates a unique microenvironment within mucosal draining lymph nodes. *Nat. Commun.* **6**, 5862 (2015).
82. Robinette, M. L. et al. IL-15 sustains IL-7R-independent ILC2 and ILC3 development. *Nat. Commun.* **8**, 14601 (2017).
83. Knolle, P. A. & Wöhlleber, D. Immunological functions of liver sinusoidal endothelial cells. *Cell. Mol. Immunol.* **13**, 347 (2016).
84. Marra, F. & Tacke, F. Roles for chemokines in liver disease. *Gastroenterology* **147**, 577–594 (2014). e571.
85. Liang, B. et al. Role of hepatocyte-derived IL-7 in maintenance of intrahepatic NKT cells and T cells and development of B cells in fetal liver. *J. Immunol.* **189**, 4444–4450 (2012).
86. Sawa, Y. et al. Hepatic interleukin-7 expression regulates T cell responses. *Immunity* **30**, 447–457 (2009).
87. Kaplan, D. H., Igyarto, B. Z. & Gaspari, A. A. Early immune events in the induction of allergic contact dermatitis. *Nat. Rev. Immunol.* **12**, 114–124 (2012).
88. Carbone, T. et al. CD56<sup>high</sup>CD16-CD62L- NK cells accumulate in allergic contact dermatitis and contribute to the expression of allergic responses. *J. Immunol.* **184**, 1102–1110 (2010).
89. Mazo, I. B. et al. Bone marrow is a major reservoir and site of recruitment for central memory CD8<sup>+</sup>T cells. *Immunity* **22**, 259–270 (2005).
90. Taniguchi, H., Toyoshima, T., Fukao, K. & Nakauchi, H. Presence of hematopoietic stem cells in the adult liver. *Nat. Med.* **2**, 198 (1996).
91. Kotton, D. N., Fabian, A. J. & Mulligan, R. C. A novel stem-cell population in adult liver with potent hematopoietic-reconstitution activity. *Blood* **106**, 1574–1580 (2005).
92. Schluns, K. S., Kieper, W. C., Jameson, S. C. & Lefrançois, L. Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. *Nat. Immunol.* **1**, 426–432 (2000).
93. Kaech, S. M. et al. Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells. *Nat. Immunol.* **4**, 1191–1198 (2003).
94. Kondrack, R. M. et al. Interleukin 7 regulates the survival and generation of memory CD4 cells. *J. Exp. Med.* **198**, 1797–1806 (2003).
95. Zhang, X., Sun, S., Hwang, I., Tough, D. F. & Sprent, J. Potent and selective stimulation of memory-phenotype CD8<sup>+</sup>T cells in vivo by IL-15. *Immunity* **8**, 591–599 (1998).
96. Becker, T. C. et al. Interleukin 15 is required for proliferative renewal of virus-specific memory CD8 T Cells. *J. Exp. Med.* **195**, 1541–1548 (2002).
97. Purton, J. F. et al. Antiviral CD4<sup>+</sup>memory T cells are IL-15 dependent. *J. Exp. Med.* **204**, 951–961 (2007).
98. Firth, M. A. et al. Nfil3-independent lineage maintenance and antiviral response of natural killer cells. *J. Exp. Med.* **210**, 2981–2990 (2013).
99. Martinez-Gonzalez, I. et al. ILC2 memory: recollection of previous activation. *Immunol. Rev.* **283**, 41–53 (2018).
100. Martinez-Gonzalez, I., Matha, L., Steer, C. A. & Takei, F. Immunological memory of group 2 innate Lymphoid Cells. *Trends Immunol.* **38**, 423–431 (2017).
101. Jing, X. et al. The formation of memory-like innate lymphoid cells 2 in allergic asthma. *J. Immunol.* **198**, 194.117–194.117 (2017).