Chapter 11
The Development and Diversity of ILCs, NK Cells and Their Relevance in Health and Diseases

Yuxia Zhang and Bing Huang

Abstract Next to T and B cells, natural killer (NK) cells are the third largest lymphocyte population. They are recently re-categorized as innate lymphocytes (ILCs), which also include ILC1, ILC2, ILC3, and the lymphoid tissue inducer (LTi) cells. Both NK cells and ILC1 cells are designated as group 1 ILCs because they secrete interferon-γ (IFN-γ) and tumor necrosis factor (TNF). However, in contrast to ILC1 and all other ILCs, NK cells possess potent cytolytic functions that resemble cytotoxic T lymphocytes (CTL). In addition, NK cells express, in a stochastic manner, an array of germ line-encoded activating and inhibitory receptors that recognize the polymorphic regions of major histocompatibility class I (MHC-I) molecules and self-proteins. Recognition of self renders NK cell tolerance to self-healthy tissues, but fail to recognize self ('missing-self') leads to activation to neoplastic transformation and infections of certain viruses. In this chapter, we will summarize the development of NK cells in the context of ILCs, describe the diversity of phenotype and function in blood and tissues, and discuss their involvement in health and diseases in humans.

Keywords NK cells • Development • NK receptors • Human disease

Abbreviations

CHILP	Common helper ILC precursor
CLP	Common lymphoid progenitor
CTL	Cytotoxic T lymphocytes
EILP	Earliest ILC progenitors

Y. Zhang (✉) • B. Huang
Guangzhou Institute of Paediatrics, Guangzhou Women and Children's Medical Centre, Guangzhou Medical University, Guangzhou, Guangdong 510623, China
e-mail: yuxia.zhang@gwcmc.org

D. Xu (ed.), *Regulation of Inflammatory Signaling in Health and Disease*,
Advances in Experimental Medicine and Biology 1024,
DOI 10.1007/978-981-10-5987-2_11

Eomes	Eomesodermin
Ets1	ETS proto-oncogene 1
Gata3	GATA-binding protein 3
ID2	Inhibitor of DNA binding 2
IFN-γ	Interferon gamma
ILC	Innate lymphocyte
ILCP	ILC progenitors
JAK1/3	Janus kinase 1/3
LTi	Lymphoid tissue inducer cells
MCMV	Murine cytomegalovirus
Mef	Myeloid elf-1-like factor
MHC-I	Major histocompatibility class I
mTOR	Mechanistic target of rapamycin
NFIL3	Nuclear factor interleukin 3
NK	Natural killer
PD-1	Programmed cell death-1
PDK1	3′-Phosphoinositide-dependent kinase 1
PLZF	Promyelocytic leukemia zinc finger
S1P1	Sphingosine-1-phosphate receptor 1
T-bet	T-cell-specific T-box transcription factor
TCF-1	T-cell factor 1
TNF	Tumor necrosis factor
TOX	Thymocyte selection-associated high-mobility group box
TRAIL	TNF-related apoptosis ligand
Zeb2	Zinc finger E-box-binding homeobox 2

11.1 NK Cells Are a Group of Innate Lymphocytes that Secrete Adaptive Immune Cytokines

The innate immune system is constituted with granulocytes, monocytes, macrophages, and dendritic cells that secrete inflammatory cytokines, as well as innate lymphocytes that secrete adaptive cytokines such as IFN-γ, interleukin (IL)-4, and IL-17. NK cells are the prototypic ILCs, and they were first described in 1975 as being able to naturally kill mouse leukemia cells [1]. Since 2008, the concept of ILCs [2] has been expanded and now includes the related subsets of NK, ILC1, ILC2, ILC3, and the lymphoid tissue inducer (LTi) cells [3]. ILCs are characterized as having lymphoid morphology but lack rearranged antigen-specific receptors and myeloid and dendritic cell phenotypical markers. ILCs develop initially from progenitors in the fetal liver [4, 5] and, later, in the adult bone marrow [6–8]. They subsequently seed mucosal tissues, where they continue to proliferate and become tissue-resident cells and maintain tissue homeostasis. ILCs and T cells share similar transcription factors that govern their differentiation and produce similar key cytokines [2, 9]. Thus, in analogy to T cells, ILCs are subdivided into cytotoxic (NK)

and all other "helper"-like subsets that resembles IFN-γ/Th1-, interleukin 4 (IL-4)/Th2-, and IL-17/Th17-secreting $CD4^+$ T helper cells [10].

11.2 ILCs Are Generated from Progenitors Downstream of the Common Lymphoid Progenitor

All ILCs initially derive from the common lymphoid progenitor (CLP). The transition from CLP to ILC-specific transcriptional program is accompanied with differential expression of over 400 genes [4, 5, 11], with temporal requirements for Nfil3 (nuclear factor interleukin 3, also known as E4bp4), TCF-1(T-cell factor 1, encoded by *Tcf7*), and ID2 (inhibitor of DNA binding 2). Nfil3 expression is essential for the development of ILC progenitors prior to their commitment, and it is induced by mesenchymal-derived IL-7 [12–14]. NFIL3 also directly activates ID2 [14, 15]. TCF-1 represses genes critical for stem cell (*Hhex* and *Lmo2*) and pro-B cell (*Spib, Irf8, Ly6d*) function [11], and its loss affects the differentiation of both NK and other ILC subsets [16–18]. ID2 induces a major regulatory shift with broad repression of progenitor cell transcription factor genes and upregulation of critical regulators including Tox (thymocyte selection-associated high-mobility group box) and Gata3 (GATA-binding protein 3) [11]. Thus, immedicably downstream of the CLP, the earliest ILC progenitor (EILP) is $TCF\text{-}1^+$ [17], which further becomes $ID2^{hi}$ common helper ILC precursor (CHILP) when NK cell potential is lost [6, 14, 19, 20]. After acquisition of promyelocytic leukemia zinc finger protein (PLZF, encoded by *Zbtb16*), ILC progenitor (ILCP) loses the capacity to differentiate into LTi cells [5, 6]. Programmed cell death-1 (PD-1) is co-expressed with PLZF and can be used as a cell surface marker to identify ILCP [11] (Fig. 11.1).

11.3 NK Cells Develop Through Immature and Mature Stages

In the adult mouse bone marrow, pre-NK cell progenitor (pre-NKP) downstream of CLP (Lin^-Flt3^+ $CD27^+CD244^+$ $CD127^+CD122^-Ly6D^-$) has a $Lin^-Flt3^-CD27^+CD244^+CD127^+CD122^-$ surface phenotype, which further develop into rNKP (recently re-defined NK progenitor) that expresses CD122 [21, 22]. CD122 couples with the common γ-chain (CD132) and forms the IL-2/IL-15 receptor, allowing NK cells to respond to IL-15 and activate JAK1/3 and STAT5 [23–25]. IL-15 also activates 3′-phosphoinositide-dependent kinase 1 (PDK1)-mTOR and regulates Nfil3 and CD122 expression [26]. rNKP develops through an immature NK cell (iNK) stage to become mature NK (mNK) cells. iNK expresses NK1.1 but does not express CD49b (antigen to DX5). The expression of Ly49 receptors on the developing iNK cells is critical for NK cell education and maturation and for the detection of

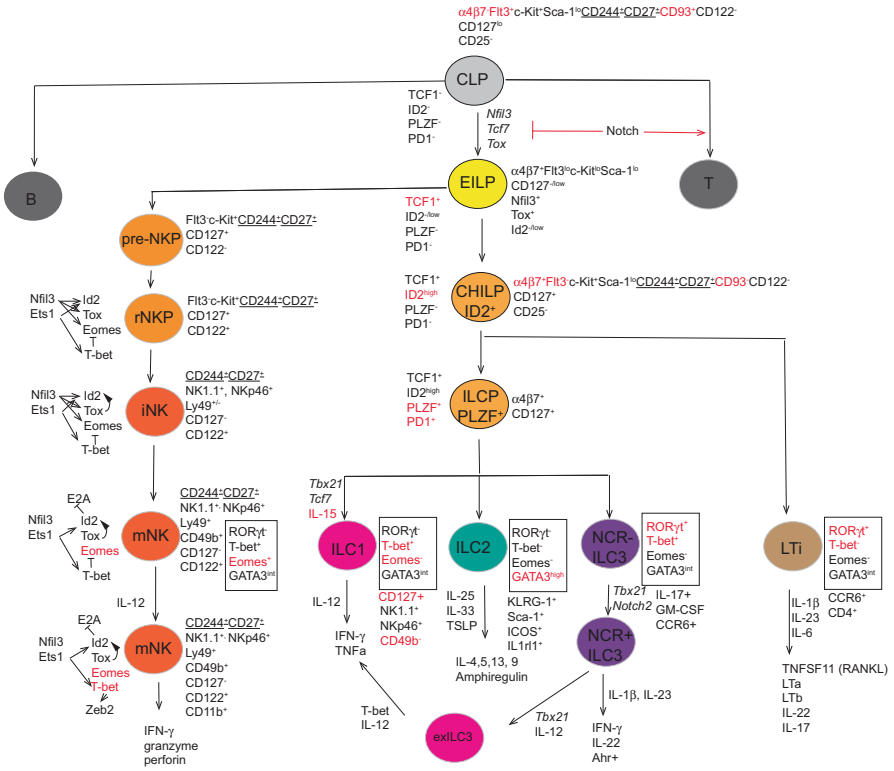

Fig. 11.1 NK and helper ILCs development in mice
T, B, NK and all other helper ILCs develop from common lymphoid progenitor (CLP). NK and ILCs development accompany with sequential differential acquirement of hundreds of transcription factors: Nfil3 and Tcf1 are required for the development and commitment of early ILC progenitors (EILP). Expression of ID2 leads to the commitment of common helper ILC precursor (CHILP), which is not able to further develop into NK cells. When PLZF is expressed, ILC progenitor (ILCP) is formed and its LTi potential is lost. Downstream of EILP, pre-NK progenitor (pre-NKP) develops into re-defined NK progenitor (rNKP) that expresses CD122, which couples with CD132 to form the IL-2/IL-15 receptor, allowing NK cells to respond to IL-15. rNKP then develops through an immature stage (iNK) to become mature NK cells (mNK). Nfil3, Tcf1, Ets1, Id2, Eomes, T-bet and Zeb2 governs NK cell development from EILP to mNK cells

invading pathogens, such as murine cytomegalovirus (MCMV) [27, 28]. The most iNK-cell-proximal mNK cells are $CD27^+CD11b^-$, produce IFN-γ and TNF-α when activated, but are not yet fully cytotoxic effector cells. Cytotoxic capacity improves with NK cell maturation by type I interferons (IFN-α or IFN-β) or proinflammatory cytokines IL-2, IL-15, IL-12, and IL-18, which upregulate CD11b through T-bet and zinc finger E-box-binding homeobox 2 (Zeb2) [29, 30]. Of note, iNK cells in the bone marrow differentiate through four stages sequentially as $CD27^-CD11b^-$, $CD27^+CD11b^-$, $CD27^+CD11b^+$, and $CD27^-CD11b^+$ [31, 32]. Besides CD11b and Dx5, mature NK cells also highly express KLRG1, CD62L, and CD43 [32].

Apart from Tcf1 and Nfil3 [8, 13–15, 17, 33] required for EILP commitment, Ets1, Id2, Eomes, and T-bet are transcription factors essential for NK cell development. Ets1, required for early NK cell lineage commitment, induces *Id2*, *Tbx21*, and *Il2rb* (CD122) expression [34–36]. Id2 suppresses E protein target genes (e.g., *Socs3*, *Tcf7*, *Cxcr5*), and the suppression of Socs3 promotes NK cell response to IL-15 [37, 38]. IL-15 is crucial for NK cell survival through the induction of the anti-apoptotic protein Bcl-2 [39, 40]. Eomesodermin (Eomes) and T-bet are members of the T-box family of transcription factors and are required by iNK and mNK cells [41]. However, tissue-resident NK cells may exhibit different developmental reliance on T-bet and Eomes [42].

NK cell maturation and function are regulated by an additional group of transcription factors. These include the Ets family protein myeloid elf-1-like factor (Mef, also known as ELF4) [43] and PU.1 (encoded by *Spi1*) [44], which respectively regulate perforin expression and NK cell proliferation in response to IL-2 and IL-12. PR domain zinc finger protein 1 (Blimp1, encoded by *Prdm1*), induced by IL-15 in a T-bet-dependent manner during early NK cell development, promotes granzyme B expression but inhibits NK cell maturation and proliferation to low concentrations of IL-15 [45]. Tox regulates mNK development partially through the induction of Id2 [46]. The Ikaros family member Aiolos (encoded by *Ikzf3*) promotes IFN-γ expression; however, its absence enhances the ability of NK cells to control tumor cells [47]. Kruppel-like factor 2 (Klf2) restricts iNK cell proliferation but is required for migration of NK cells toward IL-15-rich microenvironment [48]. IFN regulatory factor 2 (Irf2) is required for NK cell maturation in the periphery and survival in bone marrow. At homeostatic state, Gata3 is required for bone marrow NK cell maturation from $CD27^{+}CD11b^{-}$ stage and for bone marrow egress, liver migration, and IFN-γ expression. In the face of infection, Gata3-deficient NK cells demonstrated inferior control of *Listeria monocytogenes* burden in the liver [49]. However, Gata3-deficient NK cells exhibited superior activity toward MCMV due to increased CD25 expression [50]. Discrepancies regarding forkhead box protein O1 (Foxo1) exist in the literature. In one report, Foxo1 was shown to be required for iNK cell survival by inducing autophagy that removes damaged mitochondria and intracellular reactive oxygen species (ROS) [51]. In another report, however, Foxo1 inhibited late-stage NK cell maturation and function by downregulating *Tbx21* expression [52].

11.4 Tissue-Resident NK Cells Acquire Unique Phenotype and May Have Distinct Developmental Pathways

Tissue-resident NK (trNK) cells often express CD69, CD103 (αE integrin), and CD49a (α1 integrin), which are involved in retaining NK cells in the tissues. CD69 inhibits type I interferon-induced expression of sphingosine-1-phosphate receptor 1 (S1P1). S1P1 and S1P5 on NK cells binds to sphingosine-1-phosphate (S1P), which

forms a gradient with the highest concentration in peripheral blood and, thereby, promotes egress of lymphocytes from tissues into the blood [53, 54]. CD103 forms a heterodimer with β7 integrin and binds to E-cadherin on epithelial cells [55]. CD49a forms a heterodimer with β1 integrin and binds to collagen [56]. The expression of both CD103 and CD49a is regulated by transforming growth factor-β (TGF-β1) [57]. Development of trNK cells may be different from conventional blood NK cells. $CD49a^+$ $DX5^-$ $Trail^+$ trNK cells in the mouse liver express higher amount of TNF-α and GM-CSF than blood and spleen conventional NK cells, and they develop in a T-bet-dependent manner in the absence of Nfil3 [41, 42]. $CD49a^+DX5^-$ NK cells that resemble liver trNK cells are also observed in the mouse uterus and skin [42]. In contrast, salivary glands [58] and uterine NK cells [59–61] develop require Eomes in the absence of Nfil3. In addition, a population of $CD127^+$ NK cells develop in Gata3- and IL-7-dependent manner independently from T-cell precursors in the mouse thymus, and thymic trNK cells demonstrate reduced granzyme B but increased IFN-γ, GM-CSF, and TNF expression [62, 63].

11.5 NK Cell Diversity and Activity Are Regulated by Variegated Surface Receptors

The activities of NK cells are regulated by various germ line-encoded activating or inhibitory receptors (Table 11.1), many of which are expressed in stochastic patterns, resulting in many subsets of functionally distinct NK cells [64–66]. The families of NK receptors that recognize MHC class I include the murine Ly49 receptors, the primate killer cell immunoglobulin-like receptors (KIRs), and the CD94-NKG2 receptors in both rodents and primates [65]. Inhibitory receptors in humans and rodents normally contain one or more intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIM) that can activate downstream SHP-1, SHP-2, and SHIP phosphatase [67, 68]. Many of the activating receptors lack intracellular signaling motifs and transduce signals via the association with immunoreceptor tyrosine-based activating motif (ITAM)-containing adapters DAP12, FcεRγ, and CD3ζ, which recruit and activate Syk or ZAP70 tyrosine kinases [69]. NKG2D ligands are self-proteins related to MHC class I molecules. They are generally absent on the cell surface of healthy cells but are frequently upregulated upon cellular stress [70]. NKG2D recruits DAP10 and mediates signaling through the activation of PI3K [71, 72] and ERK [73]. Human KIRs contain either two (KIR2D) or three (KIR3D) extracellular immunoglobulin (Ig)-like domains. They are designated as KIR2DL or KIR3DL, respectively, if they possess a long cytoplasmic domain containing ITIM motif. KIR2DS and KIR3DS have short cytoplasmic domains lacking ITIM but associate through a charged residue in their transmembrane regions with DAP12 or FceRIγ, respectively. KIR2D receptors typically recognize human HLA-C alleles,

Table 11.1 The activating and inhibiting NK receptors on mouse and human NK cells

Activating NK receptors				Inhibiting NK receptors			
Gene	Common name	Ligand	Species	Gene	Common name	Ligand	Species
Klra4	Ly49D	H-2D^{d}	NOD Hamster	*Klra1,3,7,9*	Ly49A, C, G2, I	H-2D^{d} H2-M3	NOD B6 BALB
Klra8	Ly49H	MCMV-m157	NOD B6	*Klrb1b, d*	NKR-P1B, D	Ocil (Clr-b)	mouse
Klra16	Ly49P	MCMV	129	*Lilrb4*	Gp49b1	αvβ3 integrin	Mouse
Klrb1c	NK1.1 NKR-P1C		Mouse	*Pilra*	PILRa	O-glycosylated CD99	Mouse
Klrb1f	NKR-P1F	Clrg	Mouse	*SIGLEC-E*		Sialic acid	Mouse
Pilrb1	PILRβ	o-glycosylation CD99	Mouse	*CD244*	2B4	CD48	Mouse
ITGAL	LFA-1 CD11a	ICAM-1, 2, 3	Mouse Human	*KLRG1*	Mafa	E-, N-, R-cadherins	Mouse Human
KLRD1-KLRC2,3	CD94-NKG2C, E	Mouse Qa-1^{b}; Human HLA-E	Mouse Human	*KLRD1-KLRC1*	CD94-NKG2A	Mouse Qa-1^{b} Human HLA-E	Mouse Human
KLRK1	NKG2D	Mouse Rae-1, H60, MULT1; Human MICA, MICB, ULBP1-6	Mouse Human	*LAIR1*	LAIR-1 CD305	Collagen XVII	Mouse Human
NCR1	NKp46	Hemagglutinin	Mouse Human	*KLRB1*	NKR-P1A, CD161	LLT1 (CLEC2D)	Human
FCGR3	CD16	IgG	Mouse Human	*LILRB1*	ILT2 LIR1 CD85j	HLA-class I	Human

(continued)

Table 11.1 (continued)

Activating NK receptors				Inhibiting NK receptors			
Gene	Common name	Ligand	Species	Gene	Common name	Ligand	Species
CD226	DNAM-1	CD112 CD155	Mouse Human	*KIR2DL1-3,5*	CD158	HLA-C	Human
CD2	LFA-2	CD58	Human	*KIR3DL1,2*	CD158	HLA-Bw4 Some HLA-A	Human
CD244	2B4	CD48	Human	*CEACAM1*	CD66a	CD66	Human
CD48		2B4	Human	*SIGLEC7*	CDw328	Ganglioside GD3	Human
KLRF2	NKp65	KACL	Human	*SIGLEC9*		Sialic acid	Human
KLRF1	NKp80	AICL	Human	*SIGLEC10*		CD52	Human
NCR2	NKp44		Human	*TIGIT*		CD155/PVR CD112/Nectin-2/ CD112	Human
NKC3	Nkp30	B7-H6	Human	*CD96*		CD155	
KIR2DS	CD158	HLA-class I	Human				
KIR3DS	CD158	HLA-class I	Human				
SLAMF7	CRACC	CRACC	Human				
SLAMF6	NTB-A Ly108 CD352	NTB-A					

whereas KIR3D receptors recognize HLA-B or some HLA-A alleles [74, 75]. The NKG2 family contains one inhibitory NKG2A and two activating members NKG2C and NKG2E. The CD94-NKG2 receptors recognize nonclassical MHC-I that is HLA-E in humans and its ortholog Qa-1 in mice [76–78]. A subset of human NK cells express KIR-related inhibitory receptor, LILRB1, which recognizes a shared epitope in all human MHC class I proteins [79].

NK cells also express activating and inhibitory receptors that recognize non-MHC ligands [80]. For example, murine CD244 (2B4) recognizes CD48, an interaction essential for the IL-2-driven expansion and activation of NK cells [81]; human NKR-P1A (CD161) recognizes the lectin-like transcript-1 (LLT1, encoded by *Clec2d*), which is expressed on activated dendritic cells and B cells and inhibits NK cell cytotoxicity and IFN-γ expression [82, 83]; killer cell lectin-like receptor G1 (KLRG1) recognizes cadherins and mediates 'missing-self' education [84]; Gp49B1 recognizes αvβ3 integrin and inhibits IFN-γ expression [85, 86]. The activating DNAX accessory molecule-1 (DNAM-1, also known as CD226) [87–89] and the inhibiting T-cell immunoreceptor with Ig and ITIM domains (TIGIT) [90, 91] receptors both recognize poliovirus receptor (PVR, also known as CD155) and poliovirus receptor-related 2 (PVRL2, also known as nectin-2 and CD112), which are frequently expressed on transformed or stressed cells.

During NK cell development, the expression of self-MHC class I-reactive inhibitory receptors 'licenses' NK cells. Under physiological conditions, licensed NK cells engage through the Ly49 and KIR inhibitory receptors with MHC class I and prevent NK cells from attacking self, and this self-tolerance is mediated through the recruitment of SHP-1, SHP-2, and SHIP phosphatase [67, 68]. Interestingly, licensed NK cells are more potent in their cytotoxicity toward MHC class I-deficient target cells and secrete more IFN-γ and TNF-a under noninflammatory conditions [92, 93]. During infection, however, inhibitory receptor engagement impairs the ability of licensed NK cells to control cytomegalovirus (CMV) infection [93]. The absence of inhibitory receptors on NK cells can have a beneficiary effect in human leukemia patients receiving irradiation therapy followed by bone marrow transplantation. The absence or mismatch of donor NK inhibitory KIR receptors with recipient MHC-I was associated with better leukemic cell clearance and graft acceptance [94].

Activating receptors have the ability to recognize 'altered-self', which is often induced on malignant or stressed cells [95], and trigger NK cells to kill their targets. NK cells mediate target-cell killing by a number of mechanisms, including (1) the secretion of cytokines, (2) exocytosis of cytoplasmic granules containing perforin and enzyme, (3) FAS ligand and TNF-related apoptosis ligand (TRAIL)-mediated induction of apoptosis, and (4) CD16 cross-linking and antibody-dependent cell-mediated cytotoxicity (ADCC) [94]. However, when NK cells are chronically exposed to endogenous, as well as foreign ligands recognized by their activating receptors, they are tolerated through either receptor downregulation or hyporesponsiveness [65]. NK cell tolerance mediated by activating receptors is reversible and can be broken in the presence of inflammatory cytokines or infection. For instance, in C57BL/6 mice receiving MCMV infection, initially both licensed and

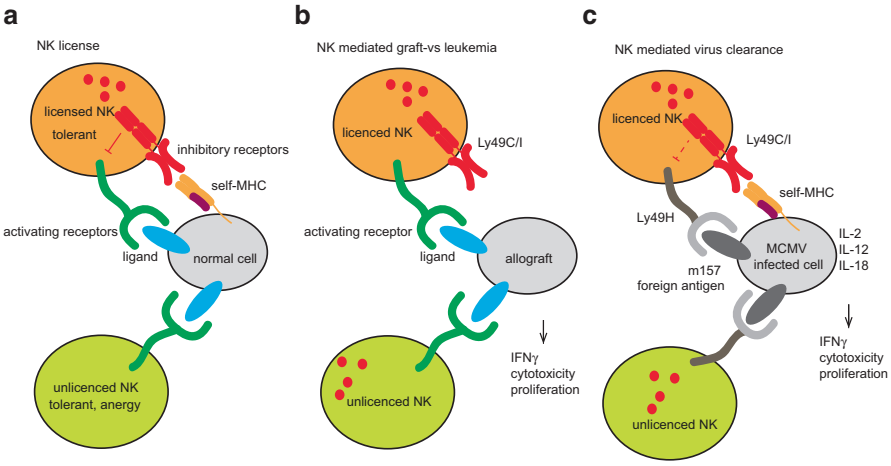

Fig. 11.2 NK cell license, activation and inhibition
(**a**) NK cell license occurs with the expression of self-MHC class I-reactive inhibitory receptors, Ly49 in mice and KIR in man. This prevents NK cells from attacking self. In the absence of inhibitory receptors, chronic exposure of activating receptors with their ligands can also render NK cell hyporesponsive. (**b**) NK cell activation takes place under instances of human leukemia patients receiving irradiation therapy followed by bone marrow transplantation. The absence or mismatch of donor inhibitory NK receptors with recipient MHC-class I promotes leukemic cell clearance by both licensed and unlicensed NK cells. (**c**) During viral infection, inhibitory receptors on licensed NK cells inhibit their proliferation burst, and under these circumstances, unlicensed NK cells are the main mediators of viral clearance

unlicensed NK cells expressed CD69 and upregulated IFN-γ and granzyme B at similar level, but, subsequently unlicensed NK cells predominated in numbers and were the main mediators of viral clearance. The engagement of the activating Ly49H receptor with MCMV-encoded glycoprotein m157 on infected cells promoted unlicensed NK cells to undergo a proliferative burst, but the inhibitory receptors on licensed NK cells restrained the proliferation through SHP-1 phosphatase signaling [68, 93] (Fig. 11.2).

11.6 NK Cells Participate in Tissue Remodeling in Humans and Undergo Clonal-Like Expansion During Viral Infection

A mouse analog of human NK progenitor has been defined as $Lin^{-}CD34^{+}CD38^{+}CD123^{-}CD45RA^{+}CD7^{+}CD10^{+}CD127^{-}$, which selectively gives rise to NK cells *in vitro* and *in vivo* [96]. Circulating human NK cells are a diverse population. In any given individual, the diversity is generated by the developmentally distinct NK cell subsets, KIR gene content, polymorphisms, and copy number variations [64], with differentiation and reprogramming in response to tissue-specific environment and infections [97]. Transcriptional, telomere length, and transfer of human NK cells

into NOD/SCID/$\gamma c^{-/-}$ mice have demonstrated that circulating NK cells in human blood display sequential $CD56^{bright}$ $CD62L^{+}$, $CD56^{dim}CD62L^{+}$ $CD94^{high}$, and $CD56^{dim}CD62L^{-}$ $CD94^{low}$ developing stages [98, 99]. $CD56^{bright}$ $CD62L^{+}$ NK cells are mostly KIR^{-} $NKG2A^{+}CD27^{dim}$ $CD57^{-}CD16^{+/-}$ but express CD127 and CD117 (also known as KIT and SCFR), which are also hallmarks of non-NK ILCs [2, 100]. Upon stimulation with combinations of IL-12, IL-15, and IL-18, $CD56^{bright}$ $CD62L^{+}$ and $CD56^{dim}CD62L^{+}$ NK cells strongly proliferate and produce significantly greater amount of IFN-γ than $CD56^{dim}CD62L^{-}$ NK cells. However, engagement of the activating receptors evokes more prominent chemokine (MIP-1α, MIP-1β and RANTES) and cytokine (IFN-γ) expression and NK cell cytotoxicity in $CD56^{dim}CD62L^{+}$ and $CD56^{dim}CD62L^{-}$ cells. [98, 101, 102]. $CD56^{dim}$ NK cells can further develop with the sequential loss of NKG2A and the acquisition of KIRs and CD57 [103]. $CD56^{dim}CD57^{+}$ NK cells have increased cytotoxic capacity than $CD56^{dim}CD57^{-}$ NK when they are activated through CD16 [104].

In parallel to mice, human tissue-resident NK cells also express CD69, CD103, and CD49a, and they may derive directly from progenitors that reside within the tissues [97]. NK cells are found at high frequencies in the endometrium of human uterus and decidua in the first trimester of pregnancy. Throughout the second half of the menstrual cycle, progesterone from the ovaries acts on uterine stromal cells, which in turn secrete IL-15 and support uterine NK cell proliferation [105]. During pregnancy, a key role for $CD56b^{right}$ uNK cells is to promote trophoblast invasion and maternal spiral artery remodeling, which is mediated through the production of IL-8, interferon-inducible protein-10 (IP10), and an array of angiogenic factors including vascular endothelial growth factor A (VEGF-A), VEGF-C, and angiopoietins [99, 106]. Critically, fetal trophoblasts, which come into direct contact with maternal blood and tissues during pregnancy, are exempt from uNK-mediated cell killing. Uterine $CD56^{bright}$ $CD49a^{+}CD103^{+}CD9^{+}$ NK cells express perforin, granzymes A and B, and the activating receptors NKp30, NKp44, NKp46, NKG2D but are unable to form mature activating synapses and thus are not cytotoxic [107, 108]. Furthermore, the high expression of inhibitory KIRs (KIR2DL1, KIR2DL2, KIR2DL3), the CD94-NKG2A receptor complex, and the LILRB1 inhibit NK cell activation through the recognition of HLA-C, HLA-E, and HLA-G expressed on the extravillous trophoblasts, respectively [107, 109]. Interestingly, primary villous trophoblasts do not express HLA, and extravillous trophoblasts are devoid of HLA-A and HLA-B.

In liver sinusoids, NK cells represent up to 30–40% of all hepatic lymphocytes [110], and $CD56^{bright}$ and $CD56^{dim}$ cells are present in equal proportions [111, 112]. Hepatic $CD56^{bright}$ NK cells express CD69 and are tissue resident [113, 114]. Liver resident macrophages (Kupffer cells) interact with NK cells to keep immune tolerance to nonpathogenic antigens from food and LPS from gut commensal bacteria, but remain alert to infections by pathogens and viruses. In recognition of bacterial cell wall products via TLR2/4 -MyD88, Kupffer cells secrete IL-10 and blunt NK cell activation [115]. However, when DNA or RNA viruses activate the TLR3-TRIF-IRF-3 [115] or TLR8 pathways [116], Kupffer cells elicit potent IFN-γ and TNF expression in $CD56^{bright}$ trNK cells. Intrahepatic NK cells also mediate target-

cell killing through the expression of TRAIL, whose expression is correlated with the control of hepatitis C virus (HCV) infection [117]. But during HBV infection, TRAIL also causes liver damage and can eliminate antigen-specific T cells [118, 119].

Clonal-like expansion and memory formation of NK cells have been observed in humans with cytomegalovirus (HCMV) [120–123], chikungunya virus (CHIKV) [124] and hantavirus [125] infections. Clonal-expanded cells are characterized by the expression of NKG2C, CD57, and activating KIRs (KIR2DS4, KIR2DS2, KIR3DS1), a general lack of the expression of inhibitory NKG2A and KIR3DL1 receptors (in individuals expressing its HLA-Bw4 ligand), and the decreased expression of CD161 (also known as KLRB1), NKp30, NKp46, and CD7. A subset of clonal-expanded NK cells can further acquire adaptive phenotypes that resembles more with cytotoxic $CD8^+$ T lymphocytes than conventional NK cells. The intronic region of *ZBTB16* in adaptive NK cells is hypermethylated, which is correlated with the decreased expression of PLZF and its target genes encoding FcεRγ, SYK, and EAT-2. Adaptive PLZF-deficient NK cells are distinct from clonal-expanded NK cells expressing CD57, NKG2C and PLZF, and produce less IFN-γ upon cytokine stimulation with IL-12 and IL-18 [126].

11.7 Conclusion

NK cells are a heterogeneous population of innate lymphocytes that develop from the common lymphoid progenitors. Tissue-resident NK cells may have different developmental origins and are phenotypically distinct from their blood counterparts. NK cells employ both inhibiting and activating receptors for 'missing-self' education, activation, and terminal differentiation. In humans, NK cells are critical for the implantation of the embryos and for the control of neoplastic transformation and viral infections, but they may also induce collateral damages to the tissues. Despite lacking rearranged antigen-specific receptors, NK cells can acquire adaptive T-cell features by clonal-like expansion and alteration in their DNA methylation profiles during viral infections.

Acknowledgments Y.Z. is supported by the Guangzhou Women and Children's Medical Center Start-up Fund (5001-3001032).

References

1. Kiessling R, Klein E, Wigzell H (1975) "Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol 5:112–117

2. Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, Mckenzie AN, Mebius RE, Powrie F, Vivier E (2013) Innate lymphoid cells—a proposal for uniform nomenclature. Nat Rev Immunol 13:145–149
3. Mebius RE, Rennert P, Weissman IL (1997) Developing lymph nodes collect CD4+CD3-LTbeta+ cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. Immunity 7:493–504
4. Chea S, Schmutz S, Berthault C, Perchet T, Petit M, Burlen-Defranoux O, Goldrath AW, Rodewald HR, Cumano A, Golub R (2016) Single-cell gene expression analyses reveal heterogeneous responsiveness of fetal innate lymphoid progenitors to notch signaling. Cell Rep 14:1500–1516
5. Ishizuka IE, Chea S, Gudjonson H, Constantinides MG, Dinner AR, Bendelac A, Golub R (2016) Single-cell analysis defines the divergence between the innate lymphoid cell lineage and lymphoid tissue-inducer cell lineage. Nat Immunol 17:269–276
6. Constantinides MG, Mcdonald BD, Verhoef PA, Bendelac A (2014) A committed precursor to innate lymphoid cells. Nature 508:397–401
7. Klose CS, Flach M, Mohle L, Rogell L, Hoyler T, Ebert K, Fabiunke C, Pfeifer D, Sexl V, Fonseca-Pereira D, Domingues RG, Veiga-Fernandes H, Arnold SJ, Busslinger M, Dunay IR, Tanriver Y, Diefenbach A (2014) Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. Cell 157:340–356
8. Yu X, Wang Y, Deng M, Li Y, Ruhn KA, Zhang CC, Hooper LV (2014) The basic leucine zipper transcription factor NFIL3 directs the development of a common innate lymphoid cell precursor. Elife 3
9. Vivier E, Van De Pavert SA, Cooper MD, Belz GT (2016) The evolution of innate lymphoid cells. Nat Immunol 17:790–794
10. Diefenbach A, Colonna M, Romagnani C (2017) The ILC world revisited. Immunity 46:327–332
11. Seillet C, Mielke LA, Amann-Zalcenstein DB, Su S, Gao J, Almeida FF, Shi W, Ritchie ME, Naik SH, Huntington ND, Carotta S, Belz GT (2016) Deciphering the innate lymphoid cell transcriptional program. Cell Rep 17:436–447
12. Geiger TL, Abt MC, Gasteiger G, Firth MA, O'connor MH, Geary CD, O'sullivan TE, Van Den Brink MR, Pamer EG, Hanash AM, Sun JC (2014) Nfil3 is crucial for development of innate lymphoid cells and host protection against intestinal pathogens. J Exp Med 211:1723–1731
13. Seillet C, Rankin LC, Groom JR, Mielke LA, Tellier J, Chopin M, Huntington ND, Belz GT, Carotta S (2014b) Nfil3 is required for the development of all innate lymphoid cell subsets. J Exp Med 211:1733–1740
14. Xu W, Domingues RG, Fonseca-Pereira D, Ferreira M, Ribeiro H, Lopez-Lastra S, Motomura Y, Moreira-Santos L, Bihl F, Braud V, Kee B, Brady H, Coles MC, Vosshenrich C, Kubo M, Di Santo JP, Veiga-Fernandes H (2015) NFIL3 orchestrates the emergence of common helper innate lymphoid cell precursors. Cell Rep 10:2043–2054
15. Male V, Nisoli I, Kostrzewski T, Allan DS, Carlyle JR, Lord GM, Wack A, Brady HJ (2014) The transcription factor E4bp4/Nfil3 controls commitment to the NK lineage and directly regulates Eomes and Id2 expression. J Exp Med 211:635–642
16. Mielke LA, Groom JR, Rankin LC, Seillet C, Masson F, Putoczki T, Belz GT (2013) TCF-1 controls ILC2 and NKp46+RORgammat+ innate lymphocyte differentiation and protection in intestinal inflammation. J Immunol 191:4383–4391
17. Yang Q, Li F, Harly C, Xing S, Ye L, Xia X, Wang H, Wang X, Yu S, Zhou X, Cam M, Xue HH, Bhandoola A (2015b) TCF-1 upregulation identifies early innate lymphoid progenitors in the bone marrow. Nat Immunol 16:1044–1050
18. Yang Q, Monticelli LA, Saenz SA, Chi AW, Sonnenberg GF, Tang J, De Obaldia ME, Bailis W, Bryson JL, Toscano K, Huang J, Haczku A, Pear WS, Artis D, Bhandoola A (2013) T cell factor 1 is required for group 2 innate lymphoid cell generation. Immunity 38:694–704

19. Klose CS, Kiss EA, Schwierzeck V, Ebert K, Hoyler T, D'hargues Y, Goppert N, Croxford AL, Waisman A, Tanriver Y, Diefenbach A (2013) A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. Nature 494:261–265
20. Seehus CR, Aliahmad P, De La Torre B, Iliev ID, Spurka L, Funari VA, Kaye J (2015) The development of innate lymphoid cells requires TOX-dependent generation of a common innate lymphoid cell progenitor. Nat Immunol 16:599–608
21. Carotta S, Pang SH, Nutt SL, Belz GT (2011) Identification of the earliest NK-cell precursor in the mouse BM. Blood 117:5449–5452
22. Fathman JW, Bhattacharya D, Inlay MA, Seita J, Karsunky H, Weissman IL (2011) Identification of the earliest natural killer cell-committed progenitor in murine bone marrow. Blood 118:5439–5447
23. Eckelhart E, Warsch W, Zebedin E, Simma O, Stoiber D, Kolbe T, Rulicke T, Mueller M, Casanova E, Sexl V (2011) A novel Ncr1-Cre mouse reveals the essential role of STAT5 for NK-cell survival and development. Blood 117:1565–1573
24. Nandagopal N, Ali AK, Komal AK, Lee SH (2014) The critical role of IL-15-PI3K-mTOR pathway in natural killer cell effector functions. Front Immunol 5:187
25. Park SY, Saijo K, Takahashi T, Osawa M, Arase H, Hirayama N, Miyake K, Nakauchi H, Shirasawa T, Saito T (1995) Developmental defects of lymphoid cells in Jak3 kinase-deficient mice. Immunity 3:771–782
26. Yang M, Li D, Chang Z, Yang Z, Tian Z, Dong Z (2015a) PDK1 orchestrates early NK cell development through induction of E4BP4 expression and maintenance of IL-15 responsiveness. J Exp Med 212:253–265
27. Babic M, Pyzik M, Zafirova B, Mitrovic M, Butorac V, Lanier LL, Krmpotic A, Vidal SM, Jonjic S (2010) Cytomegalovirus immunoevasin reveals the physiological role of "missing self" recognition in natural killer cell dependent virus control in vivo. J Exp Med 207:2663–2673
28. Lanier LL (2008) Evolutionary struggles between NK cells and viruses. Nat Rev Immunol 8:259–268
29. Kim S, Iizuka K, Kang HS, Dokun A, French AR, Greco S, Yokoyama WM (2002) In vivo developmental stages in murine natural killer cell maturation. Nat Immunol 3:523–528
30. Van Helden MJ, Goossens S, Daussy C, Mathieu AL, Faure F, Marcais A, Vandamme N, Farla N, Mayol K, Viel S, Degouve S, Debien E, Seuntjens E, Conidi A, Chaix J, Mangeot P, De Bernard S, Buffat L, Haigh JJ, Huylebroeck D, Lambrecht BN, Berx G, Walzer T (2015) Terminal NK cell maturation is controlled by concerted actions of T-bet and Zeb2 and is essential for melanoma rejection. J Exp Med 212:2015–2025
31. Chiossone L, Chaix J, Fuseri N, Roth C, Vivier E, Walzer T (2009) Maturation of mouse NK cells is a 4-stage developmental program. Blood 113:5488–5496
32. Hayakawa Y, Smyth MJ (2006) CD27 dissects mature NK cells into two subsets with distinct responsiveness and migratory capacity. J Immunol 176:1517–1524
33. Seillet C, Huntington ND, Gangatirkar P, Axelsson E, Minnich M, Brady HJ, Busslinger M, Smyth MJ, Belz GT, Carotta S (2014a) Differential requirement for Nfil3 during NK cell development. J Immunol 192:2667–2676
34. Barton K, Muthusamy N, Fischer C, Ting CN, Walunas TL, Lanier LL, Leiden JM (1998) The Ets-1 transcription factor is required for the development of natural killer cells in mice. Immunity 9:555–563
35. Lee KN, Kang HS, Jeon JH, Kim EM, Yoon SR, Song H, Lyu CY, Piao ZH, Kim SU, Han YH, Song SS, Lee YH, Song KS, Kim YM, Yu DY, Choi I (2005) VDUP1 is required for the development of natural killer cells. Immunity 22:195–208
36. Ramirez K, Chandler KJ, Spaulding C, Zandi S, Sigvardsson M, Graves BJ, Kee BL (2012) Gene deregulation and chronic activation in natural killer cells deficient in the transcription factor ETS1. Immunity 36:921–932

37. Boos MD, Yokota Y, Eberl G, Kee BL (2007) Mature natural killer cell and lymphoid tissue-inducing cell development requires Id2-mediated suppression of E protein activity. J Exp Med 204:1119–1130
38. Delconte RB, Shi W, Sathe P, Ushiki T, Seillet C, Minnich M, Kolesnik TB, Rankin LC, Mielke LA, Zhang JG, Busslinger M, Smyth MJ, Hutchinson DS, Nutt SL, Nicholson SE, Alexander WS, Corcoran LM, Vivier E, Belz GT, Carotta S, Huntington ND (2016) The helix-loop-helix protein ID2 governs NK cell fate by tuning their sensitivity to interleukin-15. Immunity 44:103–115
39. Huntington ND, Puthalakath H, Gunn P, Naik E, Michalak EM, Smyth MJ, Tabarias H, Degli-Esposti MA, Dewson G, Willis SN, Motoyama N, Huang DC, Nutt SL, Tarlinton DM, Strasser A (2007) Interleukin 15-mediated survival of natural killer cells is determined by interactions among Bim, Noxa and Mcl-1. Nat Immunol 8:856–863
40. Sathe P, Delconte RB, Souza-Fonseca-Guimaraes F, Seillet C, Chopin M, Vandenberg CJ, Rankin LC, Mielke LA, Vikstrom I, Kolesnik TB, Nicholson SE, Vivier E, Smyth MJ, Nutt SL, Glaser SP, Strasser A, Belz GT, Carotta S, Huntington ND (2014) Innate immunodeficiency following genetic ablation of Mcl1 in natural killer cells. Nat Commun 5:4539
41. Gordon SM, Chaix J, Rupp LJ, Wu J, Madera S, Sun JC, Lindsten T, Reiner SL (2012) The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. Immunity 36:55–67
42. Sojka DK, Plougastel-Douglas B, Yang L, Pak-Wittel MA, Artyomov MN, Ivanova Y, Zhong C, Chase JM, Rothman PB, Yu J, Riley JK, Zhu J, Tian Z, Yokoyama WM (2014) Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. Elife 3:e01659
43. Lacorazza HD, Miyazaki Y, Di Cristofano A, Deblasio A, Hedvat C, Zhang J, Cordon-Cardo C, Mao S, Pandolfi PP, Nimer SD (2002) The ETS protein MEF plays a critical role in perforin gene expression and the development of natural killer and NK-T cells. Immunity 17:437–449
44. Colucci F, Samson SI, Dekoter RP, Lantz O, Singh H, Di Santo JP (2001) Differential requirement for the transcription factor PU.1 in the generation of natural killer cells versus B and T cells. Blood 97:2625–2632
45. Kallies A, Carotta S, Huntington ND, Bernard NJ, Tarlinton DM, Smyth MJ, Nutt SL (2011) A role for Blimp1 in the transcriptional network controlling natural killer cell maturation. Blood 117:1869–1879
46. Aliahmad P, De La Torre B, Kaye J (2010) Shared dependence on the DNA-binding factor TOX for the development of lymphoid tissue-inducer cell and NK cell lineages. Nat Immunol 11:945–952
47. Holmes ML, Huntington ND, Thong RP, Brady J, Hayakawa Y, Andoniou CE, Fleming P, Shi W, Smyth GK, Degli-Esposti MA, Belz GT, Kallies A, Carotta S, Smyth MJ, Nutt SL (2014) Peripheral natural killer cell maturation depends on the transcription factor Aiolos. EMBO J 33:2721–2734
48. Rabacal W, Pabbisetty SK, Hoek KL, Cendron D, Guo Y, Maseda D, Sebzda E (2016) Transcription factor KLF2 regulates homeostatic NK cell proliferation and survival. Proc Natl Acad Sci USA 113:5370–5375
49. Samson SI, Richard O, Tavian M, Ranson T, Vosshenrich CA, Colucci F, Buer J, Grosveld F, Godin I, Di Santo JP (2003) GATA-3 promotes maturation, IFN-gamma production, and liver-specific homing of NK cells. Immunity 19:701–711
50. Ali AK, Oh JS, Vivier E, Busslinger M, Lee SH (2016) NK cell-specific Gata3 ablation identifies the maturation program required for bone marrow exit and control of proliferation. J Immunol 196:1753–1767
51. Wang S, Xia P, Huang G, Zhu P, Liu J, Ye B, Du Y, Fan Z (2016) FoxO1-mediated autophagy is required for NK cell development and innate immunity. Nat Commun 7:11023
52. Deng Y, Kerdiles Y, Chu J, Yuan S, Wang Y, Chen X, Mao H, Zhang L, Zhang J, Hughes T, Deng Y, Zhang Q, Wang F, Zou X, Liu CG, Freud AG, Li X, Caligiuri MA, Vivier E, Yu

J (2015) Transcription factor Foxo1 is a negative regulator of natural killer cell maturation and function. Immunity 42:457–470
53. Shiow LR, Rosen DB, Brdickova N, Xu Y, An J, Lanier LL, Cyster JG, Matloubian M (2006) CD69 acts downstream of interferon-alpha/beta to inhibit S1P1 and lymphocyte egress from lymphoid organs. Nature 440:540–544
54. Walzer T, Chiossone L, Chaix J, Calver A, Carozzo C, Garrigue-Antar L, Jacques Y, Baratin M, Tomasello E, Vivier E (2007) Natural killer cell trafficking in vivo requires a dedicated sphingosine 1-phosphate receptor. Nat Immunol 8:1337–1344
55. Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL, Brenner MB (1994) Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alpha E beta 7 integrin. Nature 372:190–193
56. Kramer RH, Marks N (1989) Identification of integrin collagen receptors on human melanoma cells. J Biol Chem 264:4684–4688
57. Cerdeira AS, Rajakumar A, Royle CM, Lo A, Husain Z, Thadhani RI, Sukhatme VP, Karumanchi SA, Kopcow HD (2013) Conversion of peripheral blood NK cells to a decidual NK-like phenotype by a cocktail of defined factors. J Immunol 190:3939–3948
58. Cortez VS, Fuchs A, Cella M, Gilfillan S, Colonna M (2014) Cutting edge: salivary gland NK cells develop independently of Nfil3 in steady-state. J Immunol 192:4487–4491
59. Boulenouar S, Doisne JM, Sferruzzi-Perri A, Gaynor LM, Kieckbusch J, Balmas E, Yung HW, Javadzadeh S, Volmer L, Hawkes DA, Phillips K, Brady HJ, Fowden AL, Burton GJ, Moffett A, Colucci F (2016) The residual innate lymphoid cells in NFIL3-deficient mice support suboptimal maternal adaptations to pregnancy. Front Immunol 7:43
60. Montaldo E, Vacca P, Chiossone L, Croxatto D, Loiacono F, Martini S, Ferrero S, Walzer T, Moretta L, Mingari MC (2015) Unique Eomes(+) NK cell subsets are present in uterus and decidua during early pregnancy. Front Immunol 6:646
61. Tayade C, Fang Y, Black GP, Paffaro VA Jr, Erlebacher A, Croy BA (2005) Differential transcription of Eomes and T-bet during maturation of mouse uterine natural killer cells. J Leukoc Biol 78:1347–1355
62. Ribeiro VS, Hasan M, Wilson A, Boucontet L, Pereira P, Lesjean-Pottier S, Satoh-Takayama N, Di Santo JP, Vosshenrich CA (2010) Cutting edge: thymic NK cells develop independently from T cell precursors. J Immunol 185:4993–4997
63. Vosshenrich CA, Garcia-Ojeda ME, Samson-Villeger SI, Pasqualetto V, Enault L, Richard-Le Goff O, Corcuff E, Guy-Grand D, Rocha B, Cumano A, Rogge L, Ezine S, Di Santo JP (2006) A thymic pathway of mouse natural killer cell development characterized by expression of GATA-3 and CD127. Nat Immunol 7:1217–1224
64. Manser AR, Weinhold S, Uhrberg M (2015) Human KIR repertoires: shaped by genetic diversity and evolution. Immunol Rev 267:178–196
65. Orr MT, Lanier LL (2010) Natural killer cell education and tolerance. Cell 142:847–856
66. Rahim MM, Makrigiannis AP (2015) Ly49 receptors: evolution, genetic diversity, and impact on immunity. Immunol Rev 267:137–147
67. Binstadt BA, Brumbaugh KM, Dick CJ, Scharenberg AM, Williams BL, Colonna M, Lanier LL, Kinet JP, Abraham RT, Leibson PJ (1996) Sequential involvement of Lck and SHP-1 with MHC-recognizing receptors on NK cells inhibits FcR-initiated tyrosine kinase activation. Immunity 5:629–638
68. Long EO (2008) Negative signaling by inhibitory receptors: the NK cell paradigm. Immunol Rev 224:70–84
69. Vivier E, Nunes JA, Vely F (2004) Natural killer cell signaling pathways. Science 306:1517–1519
70. Chan CJ, Smyth MJ, Martinet L (2014) Molecular mechanisms of natural killer cell activation in response to cellular stress. Cell Death Differ 21:5–14
71. Billadeau DD, Upshaw JL, Schoon RA, Dick CJ, Leibson PJ (2003) NKG2D-DAP10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. Nat Immunol 4:557–564

72. Zompi S, Hamerman JA, Ogasawara K, Schweighoffer E, Tybulewicz VL, Di Santo JP, Lanier LL, Colucci F (2003) NKG2D triggers cytotoxicity in mouse NK cells lacking DAP12 or Syk family kinases. Nat Immunol 4:565–572
73. Quatrini L, Molfetta R, Zitti B, Peruzzi G, Fionda C, Capuano C, Galandrini R, Cippitelli M, Santoni A, Paolini R (2015) Ubiquitin-dependent endocytosis of NKG2D-DAP10 receptor complexes activates signaling and functions in human NK cells. Sci Signal 8:ra108
74. Campbell KS, Purdy AK (2011) Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations. Immunology 132:315–325
75. Parham P (2005) MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol 5:201–214
76. Fang M, Orr MT, Spee P, Egebjerg T, Lanier LL, Sigal LJ (2011) CD94 is essential for NK cell-mediated resistance to a lethal viral disease. Immunity 34:579–589
77. Orbelyan GA, Tang F, Sally B, Solus J, Meresse B, Ciszewski C, Grenier JC, Barreiro LB, Lanier LL, Jabri B (2014) Human NKG2E is expressed and forms an intracytoplasmic complex with CD94 and DAP12. J Immunol 193:610–616
78. Wada H, Matsumoto N, Maenaka K, Suzuki K, Yamamoto K (2004) The inhibitory NK cell receptor CD94/NKG2A and the activating receptor CD94/NKG2C bind the top of HLA-E through mostly shared but partly distinct sets of HLA-E residues. Eur J Immunol 34:81–90
79. Davidson CL, Li NL, Burshtyn DN (2010) LILRB1 polymorphism and surface phenotypes of natural killer cells. Hum Immunol 71:942–949
80. He Y, Tian Z (2017) NK cell education via nonclassical MHC and non-MHC ligands. Cell Mol Immunol 14:321–330
81. Lee KM, Forman JP, Mcnerney ME, Stepp S, Kuppireddi S, Guzior D, Latchman YE, Sayegh MH, Yagita H, Park CK, Oh SB, Wulfing C, Schatzle J, Mathew PA, Sharpe AH, Kumar V (2006) Requirement of homotypic NK-cell interactions through 2B4(CD244)/CD48 in the generation of NK effector functions. Blood 107:3181–3188
82. Aldemir H, Prod'homme V, Dumaurier MJ, Retiere C, Poupon G, Cazareth J, Bihl F, Braud VM (2005) Cutting edge: lectin-like transcript 1 is a ligand for the CD161 receptor. J Immunol 175:7791–7795
83. Rosen DB, Cao W, Avery DT, Tangye SG, Liu YJ, Houchins JP, Lanier LL (2008) Functional consequences of interactions between human NKR-P1A and its ligand LLT1 expressed on activated dendritic cells and B cells. J Immunol 180:6508–6517
84. Li Y, Hofmann M, Wang Q, Teng L, Chlewicki LK, Pircher H, Mariuzza RA (2009) Structure of natural killer cell receptor KLRG1 bound to E-cadherin reveals basis for MHC-independent missing self recognition. Immunity 31:35–46
85. Castells MC, Klickstein LB, Hassani K, Cumplido JA, Lacouture ME, Austen KF, Katz HR (2001) gp49B1-alpha(v)beta3 interaction inhibits antigen-induced mast cell activation. Nat Immunol 2:436–442
86. Gu X, Laouar A, Wan J, Daheshia M, Lieberman J, Yokoyama WM, Katz HR, Manjunath N (2003) The gp49B1 inhibitory receptor regulates the IFN-gamma responses of T cells and NK cells. J Immunol 170:4095–4101
87. Bottino C, Castriconi R, Pende D, Rivera P, Nanni M, Carnemolla B, Cantoni C, Grassi J, Marcenaro S, Reymond N, Vitale M, Moretta L, Lopez M, Moretta A (2003) Identification of PVR (CD155) and Nectin-2 (CD112) as cell surface ligands for the human DNAM-1 (CD226) activating molecule. J Exp Med 198:557–567
88. Chan CJ, Andrews DM, Mclaughlin NM, Yagita H, Gilfillan S, Colonna M, Smyth MJ (2010) DNAM-1/CD155 interactions promote cytokine and NK cell-mediated suppression of poorly immunogenic melanoma metastases. J Immunol 184:902–911
89. Pende D, Spaggiari GM, Marcenaro S, Martini S, Rivera P, Capobianco A, Falco M, Lanino E, Pierri I, Zambello R, Bacigalupo A, Mingari MC, Moretta A, Moretta L (2005) Analysis of the receptor-ligand interactions in the natural killer-mediated lysis of freshly isolated myeloid

or lymphoblastic leukemias: evidence for the involvement of the poliovirus receptor (CD155) and Nectin-2 (CD112). Blood 105:2066–2073
90. He Y, Peng H, Sun R, Wei H, Ljunggren HG, Yokoyama WM, Tian Z (2017) Contribution of inhibitory receptor TIGIT to NK cell education. J Autoimmun 81:1–12
91. Stanietsky N, Simic H, Arapovic J, Toporik A, Levy O, Novik A, Levine Z, Beiman M, Dassa L, Achdout H, Stern-Ginossar N, Tsukerman P, Jonjic S, Mandelboim O (2009) The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci USA 106:17858–17863
92. Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song YJ, Yang L, French AR, Sunwoo JB, Lemieux S, Hansen TH, Yokoyama WM (2005) Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature 436:709–713
93. Orr MT, Murphy WJ, Lanier LL (2010) 'Unlicensed' natural killer cells dominate the response to cytomegalovirus infection. Nat Immunol 11:321–327
94. Yokoyama WM, Altfeld M, Hsu KC (2010) Natural killer cells: tolerance to self and innate immunity to viral infection and malignancy. Biol Blood Marrow Transplant 16:S97–S105
95. Waldhauer I, Steinle A (2008) NK cells and cancer immunosurveillance. Oncogene 27:5932–5943
96. Renoux VM, Zriwil A, Peitzsch C, Michaelsson J, Friberg D, Soneji S, Sitnicka E (2015) Identification of a human natural killer cell lineage-restricted progenitor in fetal and adult tissues. Immunity 43:394–407
97. Bjorkstrom NK, Ljunggren HG, Michaelsson J (2016) Emerging insights into natural killer cells in human peripheral tissues. Nat Rev Immunol 16:310–320
98. Juelke K, Killig M, Luetke-Eversloh M, Parente E, Gruen J, Morandi B, Ferlazzo G, Thiel A, Schmitt-Knosalla I, Romagnani C (2010) CD62L expression identifies a unique subset of polyfunctional CD56dim NK cells. Blood 116:1299–1307
99. Yu J, Mao HC, Wei M, Hughes T, Zhang J, Park IK, Liu S, Mcclory S, Marcucci G, Trotta R, Caligiuri MA (2010) CD94 surface density identifies a functional intermediary between the CD56bright and CD56dim human NK-cell subsets. Blood 115:274–281
100. Carson WE, Fehniger TA, Caligiuri MA (1997) CD56bright natural killer cell subsets: characterization of distinct functional responses to interleukin-2 and the c-kit ligand. Eur J Immunol 27:354–360
101. Cooper MA, Fehniger TA, Turner SC, Chen KS, Ghaheri BA, Ghayur T, Carson WE, Caligiuri MA (2001) Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. Blood 97:3146–3151
102. Fauriat C, Long EO, Ljunggren HG, Bryceson YT (2010) Regulation of human NK-cell cytokine and chemokine production by target cell recognition. Blood 115:2167–2176
103. Bjorkstrom NK, Riese P, Heuts F, Andersson S, Fauriat C, Ivarsson MA, Bjorklund AT, Flodstrom-Tullberg M, Michaelsson J, Rottenberg ME, Guzman CA, Ljunggren HG, Malmberg KJ (2010) Expression patterns of NKG2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. Blood 116:3853–3864
104. Lopez-Verges S, Milush JM, Pandey S, York VA, Arakawa-Hoyt J, Pircher H, Norris PJ, Nixon DF, Lanier LL (2010) CD57 defines a functionally distinct population of mature NK cells in the human CD56dimCD16+ NK-cell subset. Blood 116:3865–3874
105. Wilkens J, Male V, Ghazal P, Forster T, Gibson DA, Williams AR, Brito-Mutunayagam SL, Craigon M, Lourenco P, Cameron IT, Chwalisz K, Moffett A, Critchley HO (2013) Uterine NK cells regulate endometrial bleeding in women and are suppressed by the progesterone receptor modulator asoprisnil. J Immunol 191:2226–2235
106. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, Prus D, Cohen-Daniel L, Arnon TI, Manaster I, Gazit R, Yutkin V, Benharroch D, Porgador A, Keshet E, Yagel S, Mandelboim O (2006) Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 12:1065–1074

107. Koopman LA, Kopcow HD, Rybalov B, Boyson JE, Orange JS, Schatz F, Masch R, Lockwood CJ, Schachter AD, Park PJ, Strominger JL (2003) Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. J Exp Med 198:1201–1212
108. Kopcow HD, Allan DS, Chen X, Rybalov B, Andzelm MM, Ge B, Strominger JL (2005) Human decidual NK cells form immature activating synapses and are not cytotoxic. Proc Natl Acad Sci USA 102:15563–15568
109. Sharkey AM, Xiong S, Kennedy PR, Gardner L, Farrell LE, Chazara O, Ivarsson MA, Hiby SE, Colucci F, Moffett A (2015) Tissue-specific education of decidual NK cells. J Immunol 195:3026–3032
110. Racanelli V, Rehermann B (2006) The liver as an immunological organ. Hepatology 43:S54–S62
111. Burt BM, Plitas G, Zhao Z, Bamboat ZM, Nguyen HM, Dupont B, Dematteo RP (2009) The lytic potential of human liver NK cells is restricted by their limited expression of inhibitory killer Ig-like receptors. J Immunol 183:1789–1796
112. Marquardt N, Beziat V, Nystrom S, Hengst J, Ivarsson MA, Kekalainen E, Johansson H, Mjosberg J, Westgren M, Lankisch TO, Wedemeyer H, Ellis EC, Ljunggren HG, Michaelsson J, Bjorkstrom NK (2015) Cutting edge: identification and characterization of human intrahepatic CD49a+ NK cells. J Immunol 194:2467–2471
113. Heydtmann M, Lalor PF, Eksteen JA, Hubscher SG, Briskin M, Adams DH (2005) CXC chemokine ligand 16 promotes integrin-mediated adhesion of liver-infiltrating lymphocytes to cholangiocytes and hepatocytes within the inflamed human liver. J Immunol 174:1055–1062
114. Hudspeth K, Donadon M, Cimino M, Pontarini E, Tentorio P, Preti M, Hong M, Bertoletti A, Bicciato S, Invernizzi P, Lugli E, Torzilli G, Gershwin ME, Mavilio D (2016) Human liver-resident CD56(bright)/CD16(neg) NK cells are retained within hepatic sinusoids via the engagement of CCR5 and CXCR6 pathways. J Autoimmun 66:40–50
115. Tu Z, Bozorgzadeh A, Pierce RH, Kurtis J, Crispe IN, Orloff MS (2008) TLR-dependent cross talk between human Kupffer cells and NK cells. J Exp Med 205:233–244
116. Jo J, Tan AT, Ussher JE, Sandalova E, Tang XZ, Tan-Garcia A, To N, Hong M, Chia A, Gill US, Kennedy PT, Tan KC, Lee KH, De Libero G, Gehring AJ, Willberg CB, Klenerman P, Bertoletti A (2014) Toll-like receptor 8 agonist and bacteria trigger potent activation of innate immune cells in human liver. PLoS Pathog 10:e1004210
117. Stegmann KA, Bjorkstrom NK, Veber H, Ciesek S, Riese P, Wiegand J, Hadem J, Suneetha PV, Jaroszewicz J, Wang C, Schlaphoff V, Fytili P, Cornberg M, Manns MP, Geffers R, Pietschmann T, Guzman CA, Ljunggren HG, Wedemeyer H (2010) Interferon-alpha-induced TRAIL on natural killer cells is associated with control of hepatitis C virus infection. Gastroenterology 138:1885–1897
118. Dunn C, Brunetto M, Reynolds G, Christophides T, Kennedy PT, Lampertico P, Das A, Lopes AR, Borrow P, Williams K, Humphreys E, Afford S, Adams DH, Bertoletti A, Maini MK (2007) Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell-mediated liver damage. J Exp Med 204:667–680
119. Peppa D, Gill US, Reynolds G, Easom NJ, Pallett LJ, Schurich A, Micco L, Nebbia G, Singh HD, Adams DH, Kennedy PT, Maini MK (2013) Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell-mediated deletion. J Exp Med 210:99–114
120. Beziat V, Liu LL, Malmberg JA, Ivarsson MA, Sohlberg E, Bjorklund AT, Retiere C, Sverremark-Ekstrom E, Traherne J, Ljungman P, Schaffer M, Price DA, Trowsdale J, Michaelsson J, Ljunggren HG, Malmberg KJ (2013) NK cell responses to cytomegalovirus infection lead to stable imprints in the human KIR repertoire and involve activating KIRs. Blood 121:2678–2688
121. Guma M, Angulo A, Vilches C, Gomez-Lozano N, Malats N, Lopez-Botet M (2004) Imprint of human cytomegalovirus infection on the NK cell receptor repertoire. Blood 104:3664–3671
122. Hendricks DW, Balfour HH Jr, Dunmire SK, Schmeling DO, Hogquist KA, Lanier LL (2014) Cutting edge: NKG2C(hi)CD57+ NK cells respond specifically to acute infection with cytomegalovirus and not Epstein-Barr virus. J Immunol 192:4492–4496

123. Lopez-Verges S, Milush JM, Schwartz BS, Pando MJ, Jarjoura J, York VA, Houchins JP, Miller S, Kang SM, Norris PJ, Nixon DF, Lanier LL (2011) Expansion of a unique CD57(+) NKG2Chi natural killer cell subset during acute human cytomegalovirus infection. Proc Natl Acad Sci USA 108:14725–14732
124. Petitdemange C, Becquart P, Wauquier N, Beziat V, Debre P, Leroy EM, Vieillard V (2011) Unconventional repertoire profile is imprinted during acute chikungunya infection for natural killer cells polarization toward cytotoxicity. PLoS Pathog 7:e1002268
125. Schlums H, Cichocki F, Tesi B, Theorell J, Beziat V, Holmes TD, Han H, Chiang SC, Foley B, Mattsson K, Larsson S, Schaffer M, Malmberg KJ, Ljunggren HG, Miller JS, Bryceson YT (2015) Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function. Immunity 42:443–456 doi:10.1371/journal.ppat.1002268
126. Bjorkstrom NK, Lindgren T, Stoltz M, Fauriat C, Braun M, Evander M, Michaelsson J, Malmberg KJ, Klingstrom J, Ahlm C, Ljunggren HG (2011) Rapid expansion and long-term persistence of elevated NK cell numbers in humans infected with hantavirus. J Exp Med 208:13–21