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On the Way to Become a Natural Killer Cell

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Natural Killer (NK) cells are innate lymphocytes playing pivotal roles in host defense and immune-surveillance. The homeostatic modulation of germ-line encoded/non-rearranged activating and inhibitory NK cell receptors (NKRs) determines the capability of these innate lymphocytes to either spare "self" cells or to kill viral-infected, tumor-transformed and heterologous cell targets. However, despite being discovered more than 40 years ago, several aspects of NK cell biology remain unknown or are still being debated. In particular, our knowledge of human NK cell ontogenesis and differentiation is still in its infancy as the majority of our experimental evidence on this topic mainly comes from findings obtained *in vitro* or with animal models *in vivo*. Although both the generation and the maintenance of human NK cells are sustained by hematopoietic stem cells (HSCs), the precise site(s) of NK cell development are still poorly defined. Indeed, HSCs and hematopoietic precursors are localized in different anatomical compartments that also change their ontogenic commitments before and after birth as well as in aging. Currently, the main site of NK cell generation and maturation in adulthood is considered the bone marrow, where their interactions with stromal cells, cytokines, growth factors, and other soluble molecules support and drive maturation. Different sequential stages of NK cell development have been identified on the basis of the differential expression of specific markers and NKRs as well as on the acquisition of specific effector-functions. All these phenotypic and functional features are key in inducing and regulating homing, activation and tissue-residency of NK cells in different human anatomic sites, where different homeostatic mechanisms ensure a perfect balance between immune tolerance and immune-surveillance. The present review summarizes our current knowledge on human NK cell ontogenesis and on the related pathways orchestrating a proper maturation, functions, and distributions.

Keywords: natural killer cell, ontogenesis, hematopoietic stem cell, natural killer cell receptors, cytokines, self-tolerance, education

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INTRODUCTION

Natural Killer (NK) cells were first described as large granular lymphocytes with a natural ability to kill tumor cells without a previous activation (1). Currently, it is well-known that NK cells mediate immune-surveillance not only via cytotoxic effector-functions, but also by serving as regulatory lymphocytes able to secrete cytokines and to interact with both innate and adaptive immune cells, such as monocyte/macrophages, dendritic cells (DCs), and T lymphocytes (2–5). These activities are governed by a balance between activating and inhibitory NK cell receptors (aNKRs and iNKRs)

expressed on cell surface (6–9). Under homeostatic conditions, NK cells remain in a resting state due to the engagement of iNKRs [i.e., inhibitory Killer Immunoglobulin-like receptors (iKIRs), the C-type lectin receptor NKG2A, Ig-like transcripts (ILTs), and the leukocyte Ig-like receptors (LIRs)], that recognize a broad spectrum of classical and non-classical Human Leukocyte Antigen (HLA)-I molecules constitutively expressed of autologous "self" cells (10, 11). Viral infected, tumor-transformed or allogeneic "non-self" cells down-regulate, lack or express different HLA-I alleles, thus boosting the NK cell-mediated killing of these dangerous targets via the engagement of aNKRs, that includes Natural Cytotoxicity Receptors (NCRs) (NKp30, NKp46, and NKp44), C-type lectin receptors (NKG2C, NKG2D), DNAM-1 and activating KIRs (aKIRs) ("missing self hypothesis") (6, 12–14).

NK cells comprise two main subsets defined on the basis of CD56 and CD16 surface expression: the cytotoxic $CD56^{dim}/CD16^{pos}$ ($CD56^{dim}$) population accounting for up to 90% of circulating NK cells and the regulatory $CD56^{bright}/CD16^{neg}$ ($CD56^{br}$) NK cell subset producing high amount of pro-inflammatory cytokines, such as interferon (IFN)-γ. These two NK cell populations also differ for the expression of several NKRs that determine their ability to respond to different stimuli (15). Both genetic and environmental (i.e., infections and microbes) factors also contribute to generate NK cell diversity in terms of NKR repertoire and functions (16). Indeed, extensive flow-cytometry and mass-spectrometry data clearly showed that a large diversity in the phenotype of NK cell subsets can coexist especially at tissue levels (17–20). This heterogeneity is also associated with the different microenvironments in which NK cells develop and reside (21). However, although these cells are widely distributed in several tissues and organs of human body, most of the current knowledge on these innate lymphocytes is limited to peripheral blood (PB-) NK cells (22). In this context, how and to what extent NK cells are exchanged between blood and human tissues and which anatomic compartments host tissue-resident NK cells represent important matters of scientific debate.

In this review, we discuss our current knowledge of the several steps of human NK cell ontogenesis with a special focus on those related mechanisms regulating their development, tissue homing and residency.

TISSUE SITES OF NATURAL KILLER CELL DEVELOPMENT

The production and the maintenance of NK cells in the blood are sustained by $CD34^{pos}$ hematopoietic stem cells (HSCs). However, the exact sites of NK cell development are poorly defined, as hematopoietic cell precursors have been found in different anatomic compartments of the human body both in intra-uterine and adult lifespan (23). In the embryo and fetus the hematopoiesis takes place in the yolk sac, aorta-gonad-mesonephros region, and liver, while in adults bone marrow (BM), thymus, spleen, omentum, and liver are considered the main sites of blood cell development (24).

BM has been considered for long time the major site of NK cell generation and differentiation after birth. Indeed, this immunological niche is highly enriched of $CD34^{pos}$ HSCs and hematopoietic progenitors, including NK cell ones (25). Herein, NK cell development is supported through interactions with stromal cells, cytokines, growth factors, and other soluble molecules. However, whether NK cell ontogenesis occurs exclusively or primarily in the BM niche is still being debated.

In this regard, tissue-specific NK cell development had been reported and even the so-called NK cell "education" ensuring self-tolerance can occur in certain tissues (25). Indeed, several lines of evidence demonstrated that, while the early phases of NK cell development occur in the BM, later stages of NK cell differentiations can take place in secondary lymphoid tissues (SLTs), PB, liver, mucosa-associated lymphoid tissues (MALTs), and uterus (22, 26–29). In particular, tonsils, spleen, and lymph nodes (LNs) are considered those SLTs hosting the main extra-medullary sites of NK cell development and maturation. The para-follicular T cell regions of LNs are one of the main anatomical districts enriched with NK cells. Here, more than the 90% of tissue-resident NK cells have a $CD56^{br}$ phenotype and they are able to differentiate in mature $CD56^{dim}$ NK cells following stimulation with interleukin (IL)-2, as circulating $CD56^{br}$ NK cells (15, 30). These findings suggest that LNs might be one of the major peripheral tissue sites of NK cell development. This working hypothesis is further corroborated by other evidences showing that human LNs contain $CD34^{dim}/CD45RA^{br}$ hematopoietic precursors that likely origin from HSCs in the BM and then traffic in this SLT via the PB. Once in LNs, they can differentiate in $CD56^{br}$ NK cells upon activation mediated by LN-resident T cells (26).

The existence of $CD34^{pos}$ lymphoid precursors endowed with the ability of differentiating in NK cells *in vitro* have been also reported in human thymus (31). However, patients either affected by the Di George syndrome (32) or undergone thymectomy (33, 34) and splenectomy (35) have normal frequencies of circulating NK cells, that are also phenotypically and functionally similar to those of healthy donors (30). For that reason, thymus as well as spleen are not considered major sites of NK cell ontogenesis. Although it is possible that these unaltered frequency, phenotype and functions could be due to the redundancy of NK cell developmental pathways.

Fetal liver certainly represents one of the major tissue of NK cell development and this solid organ also retain a residual ability to generate NK cells even after birth (36). Indeed, human liver is highly enriched in tissue-resident NK cells that are phenotypically and functionally distinct from their circulating counterparts (29, 37–39). Moreover, it has been reported that human liver perfusates and biopsies contain all NK cell developmental stages from multipotent $CD34^{pos}$ hematopoietic progenitors to terminally differentiated cells. In addition, liver-resident NK cell precursors retain the ability to generate *in vitro* fully mature and functional NK cells (29). Taken together, these data further support the hypothesis that adult liver represents an important tissue site for NK cell development *in vivo* even in the adult life.

Another peripheral organ highly enriched of tissue-resident NK cells is the uterus. Here, the so-called uterine NK (uNK) cells hold a unique phenotypic/functional profile and they are present at high frequencies in the decidua to ensure mother tolerance vs. the implanted fetus. uNK cells play also a primary role in angiogenesis, tissue remodeling, and immune modulation mainly during the first trimester of pregnancy (40–42). In this regard, a population of CD34^{pos} cells able to differentiate in NK cells either following *in vitro* stimulation with several cytokines or upon co-culture with decidual stromal cells had been described in human decidua (43, 44).

Although ∼10–20% of total lymphocytes in human lungs are NK cells, they share a very similar phenotype with circulating CD56^{dim} NK cell subset and express very low levels of tissue-residency markers. This observation thus suggests that lung NK cells, different from liver and uterus, likely migrate in this tissue from the PB (21).

NATURAL KILLER CELL PRECURSORS AND ONTOGENESIS

Our current knowledge on immune cell hematopoiesis postulates that the earliest step of HSCs to undergo the NK cell differentiation relies on their commitment toward the lymphoid/myeloid lineage rather than the erythroid/megakaryocyte one. Then, CD34^{pos}/CD133^{pos}/CD244^{pos} cells acquire the expression of CD45RA to become Common Lymphoid Progenitors (CLPs), which have the potential to generate B, T and innate lymphoid cells (ILCs) (45). This process requires cell-to-cell interactions with stromal cells in the context of a peculiar microenvironment characterized by the presence of the stem cell factor (SCF), the ligand for the fms-like tyrosine kinase 3 (FLT3L), and IL-7 (46).

CLPs can then further differentiate in NK cell progenitors (NKPs) that are classified in three sequential stages of maturation named NK cell progenitors (stage 1), pre-NK cells (stage 2), and immature NK (iNK) cells (stage 3) (**Figure 1**) (47, 48). The commitment of CLPs toward NKPs had been first postulated for analogy with B and T cells progenitors and it is characterized by the down-regulation of CD34 and by the acquisition of CD122, the common IL-2 receptor subunit β shared by IL-2 and IL-15 signaling pathways. The induced expression of CD122 marks the irreversible fate of CLPs toward the NK cell differentiation (22, 49, 50). Indeed, both NKPs and pre-NK cells still express CD34 and retain the ability to differentiate in T cells, DCs and other ILCs. On the opposite, CD34^{neg}/CD122^{pos} iNK cells loose this development potential, thus representing the real NKPs (**Table 1**) (47, 51).

More recently, two distinct and additional stages of pre-NK cells have been described on the basis of their negative (stage 2a) or positive (stage 2b) expression of both IL-1β and IL-2β receptors (**Figure 1** and **Table 1**). Stage 2a is mainly enriched in certain tissues (i.e., SLTs and PB) and retains the ability to give rise to T cells and DCs, while stage 2b represents the so-called common ILC progenitors, since its commitment is restricted to the generation of ILCs, including NK cells (48, 52). The transition from stage 2b to stage 3 is then marked by the acquisition of aNKR expression (i.e., NKG2D, NKp30, and NKp46) (**Table 1**).

All the developmental stages of NKPs have been mainly characterized in the context of the BM niche. However, it is still an important matter of debate whether distinct organ-specific NKPs also exist and could undergo a "peripheral ontogeny" able to generate tissue-resident NK cells (25). In this regard, a subset of putative NKP has been recently identified in BM, PB and SLTs, where it can give rise to all members of ILC lineage. Differently from the above-mentioned stage 2b pre-NK cells, these latter NKPs are characterized by a CD34^{pos}/CD45RA^{pos}/CD38^{pos}/CD10^{pos}/CD7^{pos}/CD123^{neg}/CD127^{neg} phenotype sharing several surface markers with both stage 1 and stage 2 NKPs (53). Finally, an additional CD56^{pos} subset of CD34^{neg}/CD117^{pos} precursors able to generate NK cells and ILC3s, but not ILC2s, has been described in tonsils (54).

In our currently accepted linear model of maturation (**Figure 1**), the sequential expression of specific markers on the surface of iNK cells (stage 3) parallels the acquisition of NK cell self-tolerance and effector-functions. In particular, the shift from NKPs to mature NK cells is associated with the sequential acquired expression of CD56, CD94, and of the Killer C-type lectin receptor CD161 (55). While the functional roles of the expression of both CD161 and CD56 have not yet been fully clarified, the acquisition of CD94 surface expression is essential to allow the formation of the heterodimeric C-type Lectin receptors. Hence, the CD34^{neg}/CD117$^{pos/neg}$/CD94^{pos}/HLADR^{neg}/CD10^{neg}/CD122^{pos}/CD94^{pos}/NKp44^{low}/NKG2D^{pos}/CD161^{pos} phenotype defines mature NK cells that can be then further distinguished into in the 2 final developmental stages according to the expression of CD56 and CD16 (**Table 1**) (25, 56, 57).

CD56^{br} NK cell represents the immune-regulatory and cytokine producer stage 4, characterized by a CD34^{neg}/CD117^{low}/CD94^{pos}/CD16^{neg} phenotype (**Table 1**). More recently, 2 distinct stages 4 of NK cells have been described in SLTs: 4a and 4b stages that differ for the induced expression of NKp80 on the latter subset (58, 59). The stage 4a NKp80^{neg}/CD56^{br} NK cell subset is characterized by constitutive high expression of NKG2D, NKp30, and NKp46, CD94/NKG2A, CD161, and is not endowed with potent effector-functions (**Table 1**). On the opposite, its stage 4b counterpart can produce IFN-γ and mediate perforin-dependent cytotoxicity *in vitro* (48). Both 4a and 4b NK cell stages are then considered precursors of the terminally-differentiated and cytotoxic CD56^{dim} NK cells (stage 5) (25) (**Figure 1**). Indeed, the CD56^{br} NK cell subset does not express KIRs and CD57 and it is more immature as also confirmed by the longer length of its telomeres (60). Additional experimental evidence demonstrated that the transition from CD56^{br} to CD56^{dim} NK cells is progressive as the latter terminally-differentiated subset gradually acquires the expression of CD16, KIRs, and cytotoxic granules by generating a transitory population of CD56^{bright}/CD16^{pos} NK cells (61). During this transition, stage 4 CD56^{br} NK cells lose the expression of CD117, CD127, and CD94/NKG2A receptor, while acquiring CD94/NKG2C and down-regulating CD56 (60, 62) (**Table 1**). Finally, it has been also recently proposed that stage 5 CD56^{dim}/KIR^{pos} NK cells can be further distinguished from

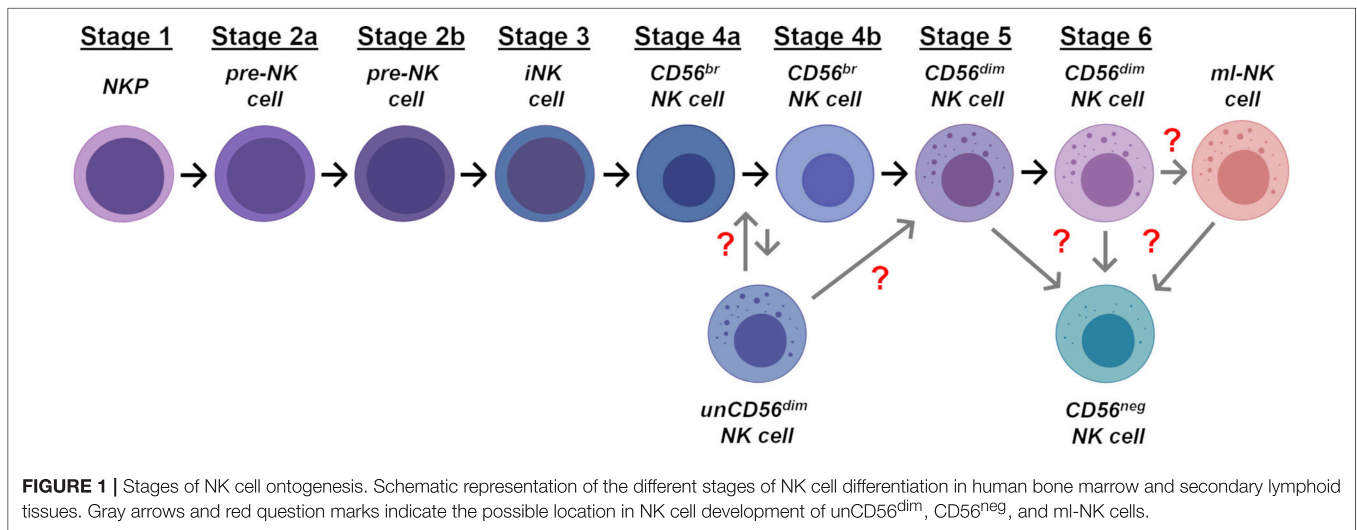

FIGURE 1 | Stages of NK cell ontogenesis. Schematic representation of the different stages of NK cell differentiation in human bone marrow and secondary lymphoid tissues. Gray arrows and red question marks indicate the possible location in NK cell development of unCD56^{dim}, CD56^{neg}, and ml-NK cells.

TABLE 1 | Principal surface markers differentially expressed on NK cell developmental intermediates.

Surface marker	Stage 1	Stage 2a	Stage 2b	Stage 3	Stage 4a	Stage 4b	Un CD56^{dim}	Stage 5	Stage 6	ml-NK	CD56^{neg}
CD34	+	+	+	−	−	−	−	−	−	−	−
CD10	+	+/−	+/−	−	−	−	n.d.	−	−	−	−
HLA-DR	+	+	+	−	−	−	n.d.	−	−	+	+
CD117	−	+	+	+	+/low	low/−	−	−	−	−	−
CD127	+	+	+	+	−	−	−	−	−	−	+
CD45RA	+	+	+	+	+/−	+/−	n.d.	−	−	−	−
IL-1 βR	−	−	+	+	+/low	low/−	n.d.	low/−	low/−	low/−	−
CD122	−	−	+	+	+	+	n.d.	+	+	+	+
CD161	−	−/low	−/low	−/+	+	+	n.d.	+	+	low/−	+
CD56	−	−	−/low	−/low	++	++	+	+	+	+	−
CD94	−	−	−	−	+	+	+	+/−	+/−	+	+
NKG2A	−	−	−	−	+	+	+	low/−	low/−	low/−	low/−
NKG2D	−	−	−	−/low	+	+	+	+	+	+	+
NKp30	−	−	−	−/low	+	+	+	+	+	low/−	low
NKp46	−	−	−	−/low	++	++	−/low	+	+	low	low
NKp80	−	−	−	−	−	+	n.d.	+	+	+	+
NKG2C	−	−	−	−	low/−	low/−	low/−	+	+	++	+/low
CD16	−	−	−	−	−	−	−	+	+	+	+
KIRs	−	−	−	−	−	−	low	+	+	+	+
CD57	−	−	−	−	−	−	−	−	+	+	+

n.d., not determined.

stage 6 based on the expression of CD57, a surface marker of replicative senescence (**Figure 1** and **Table 1**). Although this is still a matter of scientific discussion, a recent study confirmed at transcriptome, epigenome, and proteomic levels that this linear developmental trajectory starts from CD56^{br} NK cells and ends with the final acquisition of CD57 (63).

ADDITIONAL STAGES OF NK CELL MATURATION

Memory-like NK Cells

While stage 6 CD56^{dim} NK cells show a poor responsiveness to cytokine stimulation, they retain high degree of cytotoxicity and can expand in response to several viral infections (64, 65). In this regard, it has been shown that some viruses can change the NKR repertoire and can also induce the clonal expansion of peculiar NK cell subsets endowed with adaptive features. These latter populations display higher effector-functions when re-encountering the same virus and they are defined "memory-like" NK (ml-NK) cells (**Figure 1**) (16, 19, 66, 67). ml-NK cells are characterized by a peculiar KIRs^{pos}/CD57^{pos}/NKG2C^{pos} phenotype and lack the expression of CD161, NKp30, and CD7 (68–70). Among the main viruses inducing the expansion of these NK cells endowed with adaptive traits there is the Human Cytomegalovirus (HCMV) that drives a profound epigenetic reprogramming in ml-NK cells. This HCMV-driven mechanism increases the IFN-γ production when ml-NK cells are re-exposed to the same viral pathogen (71–75).

ml-NK cells have been described not only in PB but also in tissues and associated with different antigens. Indeed, a subset of a hepatic CXCR6^{pos} NK cells with adaptive properties against haptens or viral antigens had been also reported. This latter subset of ml-NK cells is liver-resident and express a CD49a^{pos}/DX5^{neg} phenotype (76, 77).

CD56^{neg} NK Cells

Besides the induced expansion of ml-NK cells, viral infections can also drive the emergence of another dysfunctional CD56^{neg}/CD16^{pos} (CD56^{neg}) NK cell subset. These cells had been firstly described during the course of HIV-1 infections and then in other viral diseases, in autoimmune-disorders and in elderly. CD56^{neg} NK cells are present at very low frequency in the PB of healthy subjects, but they represent the majority of total NK cells in AIDS patients showing high levels of HIV-1 viremia (74, 78–81). Despite being identified and characterized more than 2 decades ago, the ontogenesis of this subset is still unknown. The repertoire of NKRs expressed on CD56^{neg} NK cells shared several similarities with that of stage 3 iNK cells. However, the high constitutive expression of CD94/NKG2A, NKG2D, and CD16 together with the retention of a certain degree of cytotoxicity represent phenotypic and functional differences that do not allow a completely overlap between CD56^{neg} NK cells and stage 3 iNK cells (**Table 1**) (79, 82). Indeed, the high surface levels of KIRs, CD57 and CD107a degranulation marker on CD56^{neg} NK cells suggest that they rather represent exhausted lymphocytes that already engaged target cells (**Figure 1**) (83).

Unconventional CD56^{dim} NK Cells

The latest NK cell subset to be identified and characterized is represented by the so called unconventional NK cells holding a CD56^{dim}/CD16^{neg} phenotype (unCD56^{dim}) (84). This neglected population is extremely rare under homeostatic conditions, although it displays a significantly higher cytotoxicity compared to that of CD56^{br} and CD56^{dim} NK cell subsets. However, a very few studies characterized the homeostasis, the phenotype and the functional relevance of unCD56^{dim} NK cells subset although there is not yet a consensus on its name and classification (85–89). Unexpectedly, other and we recently reported that, in the context of the lymphopenic environment of patients affected by hematologic malignancies and undergone haploidentical stem cell transplantation (haplo-HSCT), unCD56^{dim} NK cells are by far the largest subset of NK cells immune-reconstituting in the first 2–4 weeks after the transplant (88, 90). Indeed, in this short window after haplo-HSCT the very low frequency of the conventional cytotoxic CD56^{dim} NK cells are compensated by the high expansion of unCD56^{dim} NK cells that lack the expression of CD34, CD117, and CD127 (**Table 1**). These data demonstrate that unCD56^{dim} NK cells cannot be classified as NKPs, but are rather differentiated cells expressing several NKRs as well as lytic granzyme and perforin. Moreover, the transcriptional profile of unCD56^{dim} NK cells revealed that they are placed within an intermediate stage of differentiation between CD56^{br} and CD56^{dim} NK cells as also functionally assessed with time-course *in vitro* experiments of NK cell differentiation (88). Furthermore, those unCD56^{dim} NK cells highly expanded early after haplo-HSCT also have a transient high expression of CD94/NKG2A, an iNKR also involved in NK cell differentiation. This phenomenon makes this subset anergic only in this particular human setting *in vivo*. Hence, the use of an immunotherapeutic strategy to block this inhibitory checkpoint, unleashing NK cells thus improving the clinical outcome of haplo-HSCT early after the infusion of HSCs is currently under clinical investigation (84). Taken together, these data highlight the key role played by unCD56^{dim} NK cells in the mechanisms of immune-reconstitution and also show that this unconventional NK cell subset could represent and additional or alternative stage of NK cell differentiation (**Figure 1**).

SIGNALS AND MECHANISMS REGULATING THE DIFFERENTATION OF NK CELLS

Cytokines

NK cell differentiation is finely tuned by different cytokine signals (48, 91). As previously mentioned, HSC survival and proliferation are preserved by FLT3L and SCF. Indeed, mice lacking their receptors FLT3 and c-Kit (CD117) show a consistent reduction in the frequency of CLPs (46, 92–94). In addition, the engagements of FLT3/FLT3L and c-Kit/SCF axes induce the expression of CD122 and/or IL-15Rα (CD215), thus increasing the sensitivity of NKPs to IL-15 (51, 95). Although both IL-15 and IL-2 stimulation promote the maturation of CD56^{br} toward CD56^{dim} NK cells *in vitro* (96), only IL-15 is involved in NK cell differentiation both in humans and mice.

This is confirmed by the experimental evidence showing that mature NK cells are nearly absent in mice lacking any of the 3 different subunits that compose the IL-15 heterotrimeric receptor (IL-15R) complex: CD215, CD122, and CD132 (γ_c chain) (97–101). Accordingly, patients showing an X-linked gene mutation in the γ_c gene (*il2rg*) are affected by a severe combined immune-deficiency characterized by a high susceptibility to infections due to developmental defects of lymphocytes (including NK cells) (100). Despite the γ_c chain of IL-15R is shared by other relevant cytokines (i.e., IL-2, IL-4, IL-7, IL-9, and IL-21) for their downstream signaling (102), dysfunctions of this subunit affects only the IL-15 pathway. Indeed, knockout mice lacking IL-2, IL-2Rα, IL-7, IL-7Rα, and IL-21R have normal frequencies of mature circulating NK cells (103–106).

The production of IL-15 at NK cell developmental site is mainly exerted by BM stromal and myeloid cells (107). The binding of soluble IL-15 to CD215 on the surface of surrounding cells mediates the trans-presentation of this complex to NK cells expressing CD122 and CD132 heterodimer (108–110). This engagement of IL-15R on NK cells induces the activation of JAK1/3 downstream cascade that, in turn, activates STAT3/5 and the mitogen-activated protein kinase (MAPK). These signaling pathways mediate NK cell survival via both the up-regulation of anti-apoptotic B cell lymphoma 2 (BCL-2) family members and the down-regulation of pro-apoptotic proteins (111–114). Indeed, both *Stat5*-deficient and NK cell-specific *Stat5*-deficient

mice show a marked reduction of circulating mature NK cells (115, 116). In humans, a similar severe reduction in NK cells is observed in patients with a mutation of *STAT5b*, one of the two highly conserved *Stat5* human genes (117, 118).

NK cell responsiveness to IL-15 during NK cell development is also influenced by the expression of phosphoinositide-dependent kinase-1 (PDK1) that connects IL-15 signaling to the activation of both E4BP4 (also known as Nfil3) and Inhibitor of DNA-binding 2 (ID2) transcription factors (119–121).

An additional cytokine playing a critical role in the development of NK cells is IL-21. Indeed, IL-21 stimulation *in vitro*, together with FLT3 and IL-15, promotes the differentiation and the expansion of cytotoxic CD56^{dim} NK cells from BM progenitors (104, 122). In addition, IL-21 induces rapid maturation of human NK cells and the acquisition of a KIR^{pos} mature phenotype from CD34^{pos} cell precursors (123). On the other side, IL-7 is key in promoting the survival and early differentiation of NKPs (106). As a matter of fact, although mice lacking IL-7 or its receptor (CD127) keep a relatively normal NK cell development (105), the correct engagement of CD127 expression is key in the early stages of NK cell differentiation and in the retention of NKPs in SLTs (52). Moreover, those NK cells enriched in thymus are characterized by high constitutive expression of CD127 and require IL-7 for their homeostasis (100).

IL-4 has been recently described of being able to induce the development of tissue-resident NK lymphocytes in mice by converting CD49a^{pos}/Eomes^{neg} NK cells into their functional CD49a^{pos}/Eomes^{pos} counterparts (124). Since CD49a^{pos}/Eomes^{neg} NK cell subset is considered a liver-resident NK cell subset in mice, these findings could be relevant for a better understanding of the specific tissue-resident generation of NK cells (125). However, other than expressing high levels of Eomesodermin (Eomes) transcripts, human liver-resident NK cells appear to be much more phenotypically heterogeneous compared to their murine counterparts (126).

IL-12 can also promote differentiation of NK cells and can enhance their cytotoxicity *in vitro* (127). Interestingly, an alternative pathway of NK cell development that bypasses the above-mentioned γ_c-signaling relies on the engagement of IL-12 in response to viral infections. Indeed, the stimulation of NKPs with this pro-inflammatory cytokine in the BM generates an unconventional but yet functional NK cell subset. However, this pathway is still not exploited in humans and might be highly relevant in patients with SCID (128). IL-12, together with IL-18, has been also described for its ability to induce the differentiation of ml-NK cells. In this regard, IL-12 and IL-18 have been studied as co-stimulatory factors for the generation of CMV-specific murine Ly49H^{pos} ml-NK cells (129). In particular, the IL-12/STAT4 signaling pathway is required for the formation and the expansion of these NK cells with adaptive traits (130). Similarly, the expansion of NKG2C^{pos} ml-NK cells in humans upon HCMV infection has been shown to be IL-12- plus IL-18-dependent (131, 132). In this regard, *in vitro* activation of both murine and human NK cells with IL-12, IL-18, and IL-15 supports the generation of cytokine-induced ml-NK cells (133, 134). This mechanism has been recently employed in a clinical trial to boost the expansion of adaptive NK cells showing enhanced anti-tumor responses against myeloid leukemia (135).

Transcription Factors

The commitment and differentiation of hematopoietic stem cells/precursors toward NK cell lineage require the expression of specific transcription factors (TFs). In this context, the current knowledge on NK cell development derives from experimental findings mainly generated either *in vitro* or in animal models and very little is known in human setting *in vivo*. However, it is widely accepted that several TFs are required by CLPs for their transition to both NKPs and iNK cells. These mechanisms are not specific for NK cell development as the same TFs are used to commit CLPs toward different cell lineages (136, 137). Ets-1 and PU.1, members of the Ets TF family, are involved in the transition of CLPs to NKPs and they are broadly expressed in multiple hematopoietic-derived lineages (138–141). Interestingly, Ets-1-deficient mice have a severe decrease of circulating NK cells, while knocking out PU.1 in murine models does not affect the frequency of NK cells in PB. These latter animals are also characterized by an up-regulation of Ets-1, thus suggesting the existence of compensatory mechanisms to ensure a correct ontogenesis and maturation of NK cells (142, 143).

As previously mentioned, the transition to NKPs also requires the expression of CD122 that induces STAT5 phosphorylation, dimerization and nuclear translocation (115–117). Although the specific gene targets of STAT5 in NK cells have not yet been clarified, more than 15,000 STAT5 DNA binding sites have been identified in T cells, including genes required for lymphocyte proliferation and survival (144). In addition, the expression of CD122 in NK cells is regulated by the Runx family of TFs that represent key regulators of lymphocyte lineage-specific gene expression (145, 146). In particular, Runx3 has been reported to play an important role both in NK and CD8^{pos} T cell development, thus indicating its specific involvement in transcriptional programs of cytolytic lymphocytes (146). Similarly, Thymocyte selection-associated high mobility group box protein (Tox) and the interferon-regulatory factor (IRF) families regulate the transition toward NKPs as well as toward B and T cells, ILCs and myeloid lineages (147–149). On the contrary, several other TFs regulating the early steps of NK cell differentiation are much more restricted to the development of innate lymphocytes. Indeed, E4BP4-deficient mice lack only NK cells and ILCs, as the expression of this TF is required to tune the expression of Eomes and ID2 in early progenitor cells (150–154). Other reports also claimed the existence of alternative and E4BP4-independent development pathways for immature and tissue-resident NK cells (125, 155, 156).

Another TF required for the differentiation of ILCs is ID2, whose expression is controlled by Ets-1 (138). ID2-deficient mice show a block of NK cell development between NKPs and mature NK cells with the subsequent lacking of circulating NK cells (120, 121). Recently, it has been also reported that ID2 regulates NK cell responsiveness to IL-15 through the modulation of DNA-binding helix-loop-helix E proteins (E2A) (157).

In later stages of NK cell maturation, T-box protein 21 (T-bet) and Eomes play a major role in promoting the expression of cytolytic and IFN-γ production machineries (158, 159). Indeed, mice deficient for both these latter TFs have a systemic lack of circulating mature NK cells (160, 161). However, whether or not Eomes and T-bet act in the same pathway is not yet clear as these two members of the T-box family are believed to function in a sequential manner during NK cell maturation. T-bet is required for the production of iNK and it is detectable just prior this development stage (154). Indeed, T-bet deficiency results in an accumulation of iNK cells in BM (161, 162). On the contrary, Eomes tunes the differentiation of mature NK cells from iNK cells and it is also critical to discriminate between NK and ILC1 subsets (158, 159). In addition, T-bet and Eomes have been reported to regulate NK cell development at different anatomical site as T-bet is primarily required for the production of NK cell at extramedullary sites (125, 163, 164).

SURFACE MOLECULES REGULATING NK CELL TRAFFICKING AND MATURATION

Very little is known about the mechanisms orchestrating the trafficking of human NKPs and mature NK cells from PB to tissues/organs and *vice versa* (165). Several lines of evidence indicate that this trafficking is governed by several adhesion molecules, such as integrins, selectins, and chemokine/cytokine receptors. Among them, CXCR4, the alpha-chemokine receptor specific for the stromal derived factor-1, has a role in maintaining HSCs in the BM niche (166–168). Indeed, it has been shown that the treatment with a CXCR4 antagonist promotes the progenitor mobilization from the BM (169, 170). CXCR4 appears to also play a key role in the first steps of NK cell ontogenesis since it is highly expressed by NKPs and iNK cells, while its surface levels gradually decrease during NK cell maturation (171).

Differently from CXCR4, the down-modulation of CX3C chemokine receptor 1 (CX3CR1) in response to stimulation with transforming growth factor (TGF)-β prevents the NK cell egress from the BM (172, 173). Furthermore, CX3CR1, together with CC chemokine receptors (CCRs)-7 and−5, tunes NK cell maturation as the acquisition of a CD56^{dim} phenotype is associated to its induced expression (174, 175). Similar to CX3CR1, the sphingosine-1-phosphate receptor 5 (S1P5) is involved in the NK cell release in the bloodstream and in NK cell differentiation. Indeed, terminally differentiated stage 6 NK cells up-regulate S1P5 and migrate in response to sphingosine-1-phosphate (S1P) (176). The active role of this bioactive sphingolipid in determining the NK cell trafficking is also suggested by the observation that S1P creates a gradient with highest concentrations in the blood and lymph, while its levels are maintained low in tissue parenchyma (177).

Several other adhesion molecules and chemokine receptors regulate the preferential localization of CD56^{br} and CD56^{dim} NK cells in SLTs, PB and inflamed tissues (178). Indeed, while S1P5 seems to be involved in retaining CD56^{dim} NK cells in the bloodstream, CD62L, CCR7, and CXCR3 are involved in the selective homing of CD56^{br} NK cell to LNs. Indeed, these latter surface molecules are either absent or expressed at very low levels on CD56^{dim} NK cells (30, 62, 179, 180). Furthermore, CD69 is now considered not only as a marker of cell activation, but also as a tissue-residency one. Indeed, CD56^{br} NK cells in tissues (i.e., liver, uterus, LNs) express high levels of CD69, while their counterparts in PB are CD69^{neg} (38, 181). Moreover, highly cytotoxic CD56^{dim} cells infiltrating metastatic LNs express CD69 and CCR7 and can upregulate CXCR1 (182–184). CD103 and CD49a are other tissue-residency markers that are up-regulated by NK cells in response to TGF-β (185, 186). CD103 heterodimerized with β7 and binds to E-cadherin on epithelial cells, thus retaining NK cells in tissues (187). Moreover, the heterodimer β1-CD49a is involved in the tissue retention of NK cells via the binding to collagen (188). Those CD56^{dim} NK cells preferentially migrating toward inflamed tissues, express a different patterns of cytokine/chemokine receptors that include CXCR1, CXCR2, and ChemR23 (59, 175, 189).

NK CELL EDUCATION AND ACQUISITION OF TOLERANCE TO SELF

Although NK cell ontogenesis and education are two separated processes, there are quite a few interconnections between these two key mechanisms of NK cell homeostasis. The acquired expression of iNKRs together with their binding to self-HLA molecules in BM during NK cell development represent the mechanism generating functional NK cells that are also tolerant against autologous targets (190). Indeed, the direct cell-to-cell interactions with "self"-MHC-I educate NK cells to sense the down-regulation or lack of matched HLA alleles on target cells in order to mount an efficient effector-responses only against threatening viral-infected or tumor-transformed or allogeneic targets (190–192). Hence, the so-called process of "NK cell education" relies on the avidity of binding between NKRs and self-HLA molecules and on the level of response of an NK cell to activating signals (i.e., stress ligands, inflammatory cytokines, and Fc receptor engagement) (193, 194).

In addition to the recognition of self-HLA/MHC antigens in *trans* on neighboring cells, the expression of MHC-I molecules on the NK cell itself has been shown to play an important role in regulating NK cell activity and licensing in mice, by Ly49 interaction in *cis* (195, 196). In agreement, evidences in literature indicate that KIR:HLA interactions could occur both in *trans* and in *cis* in humans too. While the HLA-I trans-presentation seems to be mainly involved in NK cell education, the *cis* interaction in humans could play a major role in the maintenance of NK cell effector potential (190). However, since, unlike Ly49, KIRs do not have a flexible stalk, it has been proposed that this *cis* interaction between HLA-C and KIR2DL could occur in endosomes rather than on the cell surface (197).

Each individual shows a highly stochastic but tolerant HLA-I specific repertoire of iNKRs, which can be shaped by the subject-specific immunological history. These phenomena are regulated by several "licensing" iKIRs, that recognize HLA-A/B/C, and by CD94/NKG2A, that binds HLA-E (9, 198, 199). During NK cell maturation, the NKR repertoire is selected to the expression of at

least one iNKRs specific for self-HLA-I haplotype on each mature NK cell. This makes NK cells able to recognize target cells, thus avoiding autoreactivity (200). CD94/NKG2A is the first HLA-I-specific iNKR expressed on differentiating NK cells prior to the appearance of KIRs. Indeed, it is present on CD56^{br} NK cells and to a less extent on CD56^{dim} NK cells (201). Moreover, *in vitro* differentiating NK cells from immature post-natal thymocytes express high levels of CD94/NKG2A that prevents the lysis of autologous cells expressing self-HLA-I alleles (202). However, it is widely accepted that iKIR^{pos} cells represent the main subset of "educated" NK lymphocytes. Indeed, during NK cell differentiation, the surface levels of CD94/NKG2A decrease while the expression of KIRs increases only on terminally differentiated CD56^{dim} NK cells (201). In this context, the human KIR gene family shows a certain degree of diversity due to both the high variability of KIR gene contents and allelic polymorphisms (203, 204). KIR and HLA genes are located on different chromosomes, and are inherited independently. This phenomenon might affect the selective evolutionary pressure as well as the NK cell-mediated susceptibility toward infections and diseases, as it is possible that KIR genes can be inherited in the absence of the cognate HLA ligand. Moreover, as previously mentioned, only NK cells expressing at least one KIR can be considered fully "licensed" (200, 205).

Although the mechanism tuning the process of NK cell education has not yet been fully disclosed, NK cell responsiveness is acquired in a finely regulated manner through KIR–KIR ligand interactions during development and several working hypotheses are currently being discussed on this matter. The first one relies on the concept of "arming" in which a given iKIR recognizes its cognate self-HLA-I allele, thus allowing the fully maturation of NK cells. In this regard, an NK cell expressing more than one iKIR should receive a stronger inhibitory signal, but this cell should also mediate a more potent alloreactivity when encountering a non-self-target (206). An opposite theory is instead based on the idea that NK cells expressing iKIRs mismatched with self HLA-I alleles are not clonally deleted, but are rather kept "unlicensed" both in PB and tissues in a state of hypo-responsiveness to ensure self-tolerance (194, 207, 208). This so called "disarming" working hypothesis states that, in the absence of self-iKIRs, the chronic stimulation of a still undetermined aNKR is associated with NK cell anergy (207).

An additional iNKR involved in NK cell education is ILT2/LIR1, which recognizes HLA-G and other shared epitopes present in all human HLA-I molecules. It has been shown that the expression of LIR1 by NK cells is able to prevent the secretion of IFN-γ (199). This iNKR appears to be expressed by mature NK cells and its surface level increases upon cytokine stimulation or HCMV infection, thus representing a possible escape mechanism from NK cell immune-surveillance (209–211). Moreover, the LIR1-mediated inhibition of NK cell effector-functions has been proposed to be also important in regulating the maternal-fetal immune tolerance during pregnancy (212).

Besides HLA-I specific iNKRs, several additional surface molecules have been reported to be involved in NK cell licensing to prevent their cell activation against self-cells. These additional mechanisms likely ensure a multi-layered and complementary system of immune tolerance and education of NK cells. In this context, the appearance of NKp46 and NKp30 before HLA-I specific iNKRs during development could ensure an HLA-I independent self-tolerance at early stages of NK cell differentiation (198, 213, 214). This hypothesis is also supported by clinical evidence in human HLA-I-deficient individuals, in which NK cells do not kill autologous cells although the engagement of HLA-specific iNKRs is either impaired or lacking (215, 216). In line with this last theory, it has been demonstrated that 2B4 could be involved in NK cell education by being expressed early on the CD34^{pos} NKPs. As a matter of fact, although 2B4 is an aNKR in mature NK cells, it can exert an inhibitory function when expressed on immature NK cells (198, 213).

Finally, another mechanism possibly preventing NK cell autoreactivity relies on the differential/asynchronous expression of NK cell receptors and ligands. A classic example is the expression of NKG2D, an aNKR able of modulating NK cell receptor activation with different thresholds (217). In adults, it has an important role in eliminate potentially dangerous cells expressing NKG2D ligands including tumor-transformed and viral-infected target cells. On the contrary, NKG2D is not expressed in embryonic life, when the soluble and exosome-bound ligands MIC-A and MIC-B are produced by human placenta. This mechanism thus contributes to prevent the activation of mother NK cells against the fetus (218, 219).

CONCLUDING REMARKS

Although our current knowledge on the mechanisms tuning human NK cell ontogenesis greatly advanced over the past 2 decades, several questions still remain unanswered. In particular, the signals and pathways involved in NK cell development in SLTs and in other anatomic compartments remain to be clarified. Furthermore, the intracellular processes by which an NK cell is able to discern between self and non-self are still elusive. Emerging evidence from high-throughput technologies highlighted that NK cell diversity is more complex than expected and it is determined by genetic and environmental determinants. Thus, it is possible that this phenotypic NK cell diversity and apparent redundancy, within the same tissue and between the different tissues, could be the result of NK cell plasticity and could mirror the different NK cell functional properties rather than mere developmental intermediates.

Future efforts in understanding NK cell differentiation, effector-functions and heterogeneity in both physiological and pathological conditions will provide insights for the prevention and the treatment of human diseases. In particular, a better understanding of NK cell development in malignancies and other diseases will facilitate the design and implementation of NK cell-mediated immunotherapies.

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