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Natural killer cell regulation - beyond the receptors

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Abstract

Natural killer (NK) cells are lymphocytes that are important for early and effective immune responses against infections and cancer. In the last 40 years, many receptors, their corresponding ligands and signaling pathways that regulate NK cell functions have been identified. However, we now know that additional processes, such as NK cell education, differentiation and also the formation of NK cell memory, have a great impact on the reactivity of these cells. Here, we summarize the current knowledge about these modulatory processes.

Introduction

In the mid-1970s, a novel immune cell type was described based on its ability to lyse allogeneic tumor cells without the need for prior sensitization. The term "natural cytotoxicity" was introduced to describe this feature and the cells mediating this effect were named NK cells [1–5]. In the last 40 years, much progress has been made in the understanding of the function and regulation of NK cells. We now know that NK cells contribute to effective innate immune responses and provide the first important line of defense against parasites, viruses and cancer [6–10]. NK cells derive from the common lymphocyte progenitor, but they are independent of a functional thymus and rely on germ-line-encoded surface receptors that do not undergo somatic recombination. One important step for the understanding of NK cell regulation was the realization that NK cells preferentially kill cells with low or no major histocompatibility complex (MHC) class I expression that led to the formulation of the "missing-self hypothesis" [11,12]. This concept was later supported through the identification of MHC class I-specific inhibitory receptors, such as Ly49 receptors in mice and killer cell immunoglobulin-like receptors (KIRs) in humans [13–19]. These inhibitory receptors possess immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic tail that are phosphorylated upon binding to MHC class I. This leads to binding and activation of phosphatases, such as SHP1/2 and SH2 domain-containing inositol 5-phosphatase (SHIP), which in turn interfere with activating signaling pathways by dephosphorylation [20], effectively preventing NK cell activation.

NK cells are stimulated by a number of different activating receptors that can recognize a variety of ligands on potential target cells [21]. Engagement of these activating receptors can trigger NK cell functions via different signaling pathways [22–24]. Despite the diversity of these early signaling pathways, inhibitory receptors can effectively control NK cell activation [9,25]. It is, therefore, now generally accepted that NK cell activity is tightly regulated by an interplay between activating and inhibitory cell surface receptors. However, in recent years, it has become clear that this is not the only level at which the activity of NK cells is regulated. The fact that the triggering of the same receptor in individual NK cells does not necessarily lead to the same outcome already implies the presence of additional mechanisms for the regulation of NK cell functions. In the following article, we will describe three additional levels of NK cell regulation.

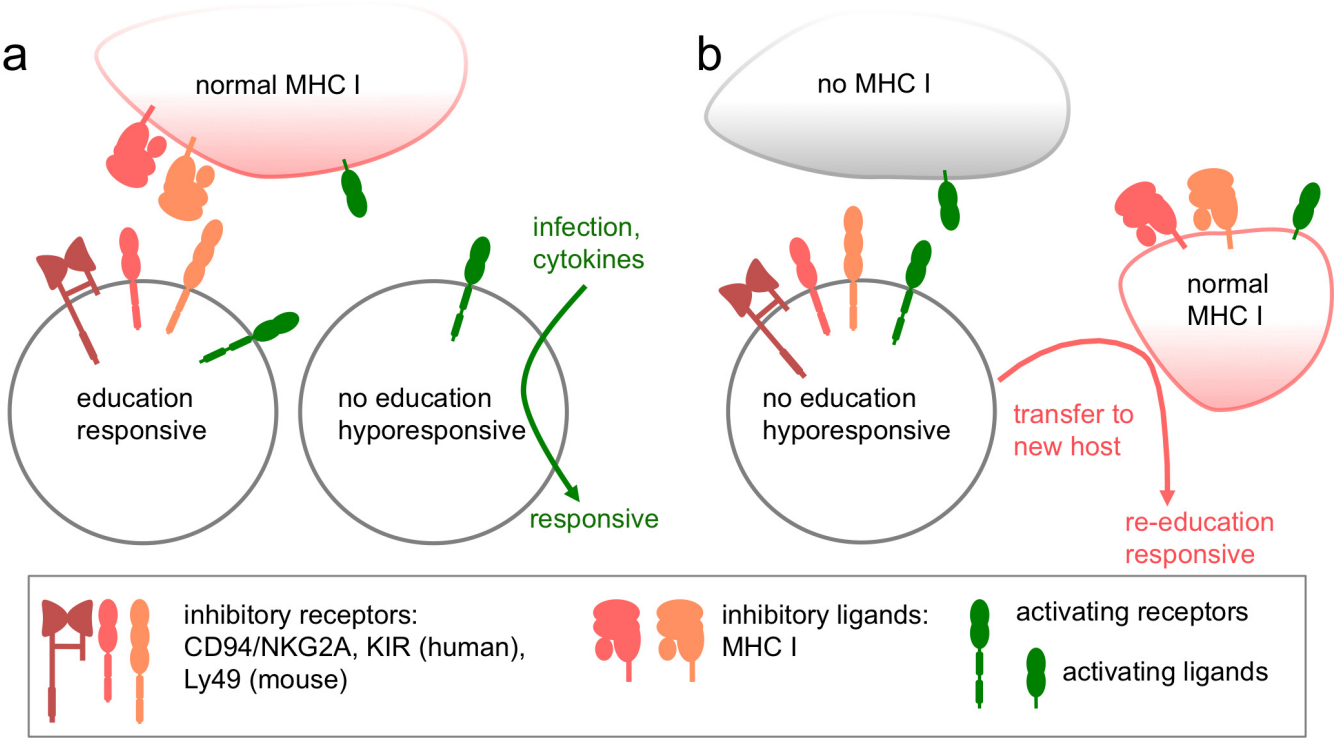
NK cell education

In accordance with the missing-self hypothesis, the "at least one" model was proposed [26]. This model assumed that NK cells need to express at least one inhibitory receptor that is specific for self-MHC class I in order to

prevent autoreactivity. This hypothesis was supported by data from human NK clones that were all found to express at least one self-specific inhibitory receptor [27]. However, it was also known that NK cells from MHC class I-deficient hosts were not autoreactive despite the lack of ligands for the inhibitory receptors [28,29]. This already suggested that additional mechanisms must exist to ensure that NK cells are not autoreactive in the absence of inhibitory signaling. Indeed, it was later discovered that a significant subset of NK cells present in healthy mice and humans lack self-specific inhibitory receptors [30–32]. These NK cells were not autoreactive and were found to be hyporesponsive when triggered through activating receptor stimulation. This adaptation of the reactivity of NK cells depending on the inhibitory receptor ligand matches is generally referred to as NK cell education [26] (Figure 1) and assures the self-tolerance of NK cells.

Initially, two opposing mechanisms were discussed on how NK cells can become educated. In the "arming" or "licensing" model, NK cells are assumed to be inactive by default and only acquire their full functionality through the engagement and the signaling of an inhibitory receptor [33,34]. In the "disarming" model, NK cells are active by default but are rendered hyporesponsive or anergic through the continuous stimulation via activating receptors recognizing endogenous ligands. They can only maintain their functionality if this chronic stimulation is counteracted by signals of inhibitory receptors [34]. While inhibitory receptors have opposite functions in both models, the outcome would be comparable – only NK cells with an inhibitory receptor for self-MHC class I can become functionally active. Additionally, the education of NK cells is not an all or nothing decision, but can be tuned in a quantitative way. The stronger the inhibitory interaction(s) of an NK cell is, the stronger it responds to activating receptor signals [35,36]. Therefore, the rheostat model has been proposed [37]. This model does not replace but rather supplements the arming or the disarming model, and describes NK

Figure 1. NK cell education: adaption of the responsiveness depending on inhibitory receptor - ligand interactions



(a) In normal major histocompatibility complex (MHC) class I-sufficient individuals (humans and mice), NK cells expressing inhibitory receptors recognizing those MHC class I molecules become educated. Those cells are responsive to activating receptor stimulation. The subset of NK cells that lacks inhibitory receptors for self MHC class I are non-educated and hyporesponsive when triggered through activating receptor stimulation. Under certain conditions, such as infections or cytokine stimulation, this subset can become responsive.
(b) In MHC class I-deficient individuals, NK cells are non-educated and hyporesponsive due to the lack of inhibitory ligands. After transfer to a new MHC class I-sufficient host, NK cells can become "re-educated" and responsive if they express the matching inhibitory receptors.
KIR, killer cell immunoglobulin-like receptor.

cell education as a dynamic process, rather than an on/off state.

With the data available today, both the arming and the disarming models are able to explain the observed phenotypes, but the mechanism remains unclear. The pros and cons of the different models have been extensively discussed [38,39]. It is not only inhibitory receptors that can dictate the reactivity of NK cells. The constitutive expression of a ligand for an activating NK cell receptor in mice results in the hyporesponsiveness of NK cells expressing the matching activating receptor [40,41]. This finding that chronic stimulation can render NK cells hyporesponsive would support the "disarming" model. Since many activating NK cell receptors are capable of recognizing endogenous ligands, NK cells probably have an individual activation threshold that is adjusted to their receptor expression and the available ligands [42]. Most importantly, these mechanisms must avoid autoreactivity while retaining maximal responsiveness of the NK cells toward infected or transformed cells.

While the functional mechanism of education is still unknown, we know from various studies that education is not final. The changes caused in educated and in hyporesponsive, uneducated cells are reversible, suggesting that there is plasticity in the education process. After transfer to an MHC-I0-sufficient environment, previously uneducated NK cells gained functional competence, whereas previously educated NK cells were rendered hyporesponsive in an MHC-I-deficient environment [43,44] (Figure 1). Similarly, non-educated human NK cells were shown to acquire functional inhibitory receptor expression upon stimulation with pro-inflammatory cytokines, which resulted in an educated phenotype [45]. Since this "re-education" is possible with mature cells and happens within a few days, it is likely uncoupled from the process of NK cell development in the bone marrow. However, findings from hematopoietic stem cell transplantations in humans suggest that the education of the donor NK cells remains even if the host MHC class I environment is different [46]. This would argue that at least in this setting, the cell responsible for the education of NK cells is of hematopoietic origin.

To complicate things even further, some inhibitory Ly49 receptors can also interact with their MHC class I ligand on the same cells *in cis* [47]. The importance of this *cis* binding for NK cell education is controversial. At least for some inhibitory receptors, it has been demonstrated that binding *in cis* contributes to this education [48,49], and the strength of the binding correlates with the potency of education [50]. However, in another experimental setup, only the interaction *in trans* was effective for the education of NK cells [51]. Additionally, the fact that NK cells can adjust their reactivity through a change in their MHC class I environment supports the importance of the *trans* interactions for the re-education [43,44].

Why are NK cells that lack sufficient inhibitory receptors for self-MHC class I only rendered hyporesponsive and why are they not deleted as in the case of autoreactive T cells? The answer to this question could be that under certain circumstances, non-educated NK cells can be beneficial to the host. During an acute virus infection, the non-educated NK cells can become functional under the influence of pro-inflammatory cytokines and can even be more efficient than educated NK cells [52] (Figure 1). Similarly, non-educated NK cells can be more effective in mediating antibody-dependent cellular cytotoxicity in neuroblastoma patients treated with an anti-GD2 antibody [53]. Under these circumstances, the lack of inhibition may make the non-educated NK cells the better effector cells.

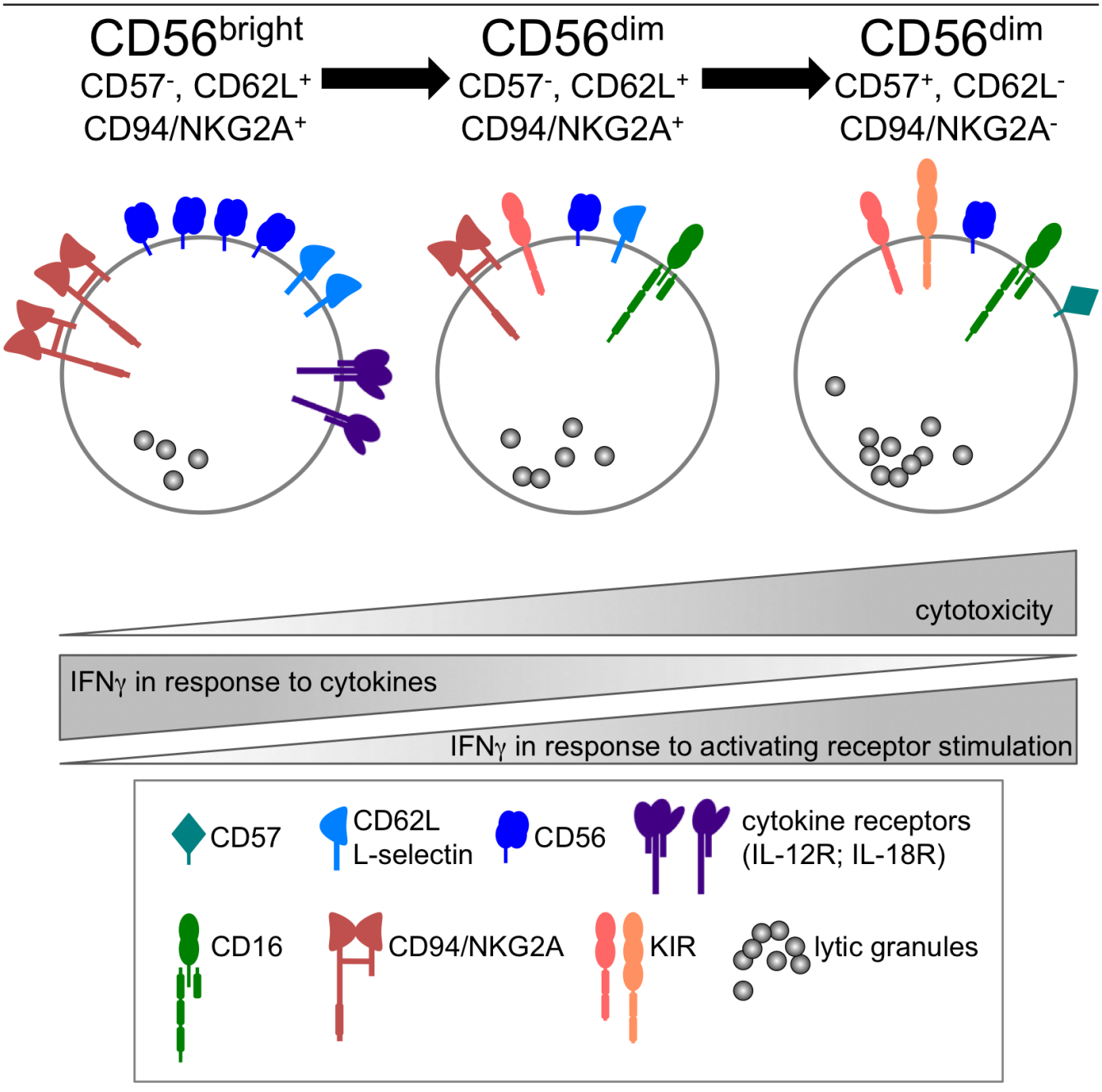
What is the molecular mechanism that determines the reactivity of educated NK cells? Interestingly, there are only a few transcriptional changes when comparing educated with non-educated NK cells [54]. One possible mechanism that could cause these functional differences without the need for changes in gene expression is the organization of receptors in the membrane. Nanoscopic analysis revealed that in educated NK cells, activating receptors were localized in nanodomains, whereas they were confined to an actin meshwork in non-educated cells [54]. In those nanodomains, the activating receptors could have the proper environment of signaling molecules needed for efficient NK cell activation [55]. This would be consistent with the finding that the triggering of activating receptors in educated NK cells results in an efficient activation of the integrin lymphocyte function-associated antigen 1 via inside-out signaling, thereby promoting the adhesion of educated NK cells to target cells [56].

NK cell differentiation and subsets

After the initial process of NK cell education, functionally competent NK cells can be found in the periphery. However, not all educated NK cells have the same functionality. Traditionally, human peripheral blood NK cells are divided in two functionally distinct subsets: $CD56^{dim}$ and $CD56^{bright}$ NK cells [57–59]. In recent years, it became clear that $CD56^{dim}$ NK cells can be further subdivided based on the expression of CD62L, CD57, or CD94/NKG2A [60–64]. Additionally, there is a developmental relationship between the different subpopulations, suggesting a differentiation of mature NK cells

starting from $CD56^{bright}$ via $CD56^{dim}$, $CD57^-$, $CD62L^+$, $CD94/NKG2A^+$ to the more differentiated $CD56^{dim}$, $CD57^+$, $CD62L^-$, $CD94/NKG2A^-$ NK cells [60–67] (Figure 2). Along this differentiation pathway, the functionality of NK cells change [68,69]. While $CD56^{bright}$ cells are not very cytotoxic, they are especially good at producing IFNγ after stimulation with pro-inflammatory cytokines, such as interleukin (IL)-12 and IL-18. This activity is gradually lost during the differentiation towards the more cytotoxic $CD56^{dim}$, $CD57^+$ NK cells. In contrast, these most differentiated NK cells can produce more interferon gamma (IFNγ) when triggered via activating

Figure 2. Adaption of NK cell reactivity during differentiation



Functionally distinct subsets of human NK cells differ in their surface receptor expression and their reactivity towards activating receptors triggering or cytokine stimulation. See text for details.

IFN, interferon; IL, interleukin; KIR, killer cell immunoglobulin-like receptor.

surface receptors [70] and this IFNγ competence has recently been linked to the epigenetic remodeling of the IFNG promoter [71]. Therefore, the functionality of NK cells changes during their differentiation (Figure 2), which may be important for the orchestration of successful NK-mediated immune responses. Recently, a study identified several thousand distinct subpopulations of NK cells in the peripheral blood of humans [72]. If this is reflected in additional differences in functionality, this will have to be addressed.

Memories of an NK cell

Recent studies have shown that NK cells can also acquire memory or memory-like functions, thereby challenging the classical distinction between innate and adaptive immunity [73]. As there are already excellent reviews about NK cell memory [73–76], we just want to briefly summarize the current knowledge about the different forms of NK cell memory that have been described so far (Table 1).

Liver-restricted memory NK cells

NK cells that exhibit a more potent secondary response were first described in a mouse model of delayed-type hypersensitivity (DTH) using hapten or viral antigens [77,78]. Recombination-activating gene (RAG)-deficient mice, lacking T and B cells, were sensitized with a hapten or a viral antigen and showed an NK cell-specific DTH response when challenged later with the same antigen. This antigen-specific type of NK cell memory is confined to CXCR6-positive liver NK cells [78,79]. However, it is currently unclear which receptors are responsible for the antigen-specific response and how liver NK cells can mediate specific and localized immune reactions at the site of antigen re-challenge.

CMV-specific memory NK cells

In another form of antigen-specific NK cell memory, the receptor responsible for the effect is known. Cytomegalovirus (CMV) infections in mice have been shown to induce a rapid and clonal-like expansion of a NK cell subset expressing Ly49H, which recognizes the CMV-encoded protein m157 [80]. These NK cell memory subsets show enhanced immune responses upon secondary challenge with CMV. The activating receptor DNAX accessory molecule-1 (CD226) cooperates with Ly49H for the expansion of these memory NK cells by signaling through Fyn and protein kinase Cη (PKCη [81]. Additionally, the expansion of CMV-specific memory NK cells is dependent on IL-12 and IL-15 and the subsequent signaling via signal transducer and activator of transcription 4 (STAT4) [82,83]. This induces the transcription factor zinc finger and BTB domain containing 32 (Zbtb32), which was shown to be essential for the proliferation and the protective capacity of the virus-specific NK cells [84]. Finally, the pro-apoptotic factor Bim is responsible for the contraction of the expanded Ly49H$^+$ NK cells population, resulting in mature, murine CMV-specific memory NK cells [85].

CMV infection is also associated with the generation of memory NK cells in humans, where the expansion and long-term persistence of NKG2C$^+$ NK cells can be observed [86,87]. However, NKG2C does not seem to be involved

Table 1. Characteristics of NK cell memory in different models Comparison of the four major types of NK cell memory. Lymphopenia-induced memory NK cells are not shown. See text for details

Memory type	Liver	CMV	FcεRγ Deficiency	Cytokine-induced
Subpopulations	Thy1+CD11b+CD27- Thy1+Ly49C/I+ [78,116] CXCR6+ [78] CD49a+DX5-[79]	Mouse: Ly49H+ [80] Human: NKG2C+ [86] CD57+ [92]	CD57dimFcεRγ- [100]	CD25+ [107]
Antigen	Haptens or viral antigens [78,117]	m157 [80]	(m157?)	-
Proliferation	No [77]	Yes [80]	Unknown	Yes [96]
Involved cytokines	IL-12 [106] CXCL16 [78]	IL-12, IL-15 [82]	IL-12?	IL-12, IL-15, IL-18 [94]
Signaling	IL-12R [106] CXCR6 [78] NKG2D [77]	IL-12R /STAT4 [82] IL-15R CD25 [108] Ly49H/DAP12 [80] DNAM-1 via Fyn, PKC [81] Zbtb32 [84] Bim [85] miR-155 [110]	IL-12R?	IL-12R /STAT4 IL-15R IL-18R CD25 [107] miR-155 [112]
Memory effect	DTH	Enhanced cytotoxicity and IFNγ production	Enhanced IFNγ production and ADCC	Enhanced IFNγ production

ADCC, antibody-dependent cellular cytotoxicity; DTH, delayed-type-hypersensitivity; IL, IFNΦΦinterferon; interleukin; PKC, protein kinase C; STAT4, signal transducer and activator of transcription 4.

in the direct recognition of CMV [88]. Interestingly, similar expansions of NKG2C$^+$ NK cells have been observed during and after other virus infections, such as hantavirus, HIV and hepatitis B [89–91], but they were always restricted to human CMV-seropositive individuals. Additionally, these NKG2C$^+$ NK cells are also positive for CD57 [92,93], demonstrating a terminal differentiation of these human CMV-dependent memory NK cells.

Cytokine-induced memory-like NK cells

In vitro exposure of NK cells to a combination of IL-12, IL-15 and IL-18 generates memory-like cells that show enhanced effector functions [94–96]. *In vivo*, inflammation or other immune responses could result in the exposure of NK cells to these cytokines. Dendritic cells are the main producers of IL-12 and IL-18, thereby regulating NK cells [97]. In a recent study, adoptive co-transfer of NK cells with dendritic cells without exogenous cytokines showed increased tumor infiltration relative to NK cell transfer alone [98]. Additionally, the improved effector functions of cytokine-exposed NK cells might be a valuable tool in enhancing the effectiveness of NK cell-based therapies against tumors [94,96,99].

Finally, there have been other reports describing NK cells with certain memory-like phenotypes. While they may be related to the types of memory described above, we list them here as separate examples of NK cell memory.

FcεRγ-deficient memory NK cells

A subpopulation of human NK cells has been described that is deficient for the FcεRγ signaling adaptor. In NK cells, FcεRγ is a signaling partner chain for CD16, an activating Fc receptor responsible for the recognition of antibody-coated cells. NK cells lacking FcεRγ display poor cytotoxicity but significantly enhanced IFNγ production upon CD16 stimulation [100]. FcεRγ$^-$ NK χελλσ have a CD56^{dim} phenotype and the existence of this subset is also associated with prior human CMV infection. However, these NK cells also demonstrate enhanced responses against other viruses [101].

Lymphopenia-induced long-lived NK cells

In a lymphopenic environment (e.g., Rag2$^{-/-}$ IL2rγ$^{-/-}$ mice), NK cells undergo a rapid but non-specific proliferation after adoptive transfer and, similar to memory T cells, show self-renewal at a steady state. These NK cells are able to respond robustly to viral infection more than 6 months after transfer [102–105].

How does NK cell memory work?

It is likely that the different forms of NK cell memory described above are not mutually exclusive and independent phenomena. Rather, there are some common denominators that suggest that they are connected and possibly represent different forms of common "memory NK cells". The signaling via pro-inflammatory cytokines seems to be important for the generation of NK cell memory. IL-12 in particular is essential for the generation of CMV-specific memory NK cells [82], for cytokine-induced memory NK cells, likely also for the generation of liver-restricted memory NK cells [106] and is possibly important for FcεRγ$^-$ memory NK cells. IL-12 induces the expression of a high-affinity IL-2 receptor via the up-regulation of the IL-2Rα chain (CD25) [107,108], which might serve as an early marker for memory NK cells. However, the molecular basis for the increased IFNγ production and the (in some cases) enhanced cytotoxicity of memory NK cells is still unclear. Analysis of gene expression data show specific differences between resting, activated and CMV-induced memory NK cells and suggests a common transcriptional program that is conserved in the memory differentiation of NK cells and CD8$^+$ T cells in response to infection [109]. Additionally, microRNAs (miRNA) have been shown to play a role in the regulation of NK cell functions, and the upregulation of miRNA-155 has been observed in CMV and cytokine-induced memory NK cells [110–112]. Finally, memory NK cells often display a more differentiated phenotype with the expression of CD57 and KLRG1 [92,93]. As described above, NK cells gain IFNγ-competence in response to activating receptor triggering when they mature, which is connected to a partial epigenetic remodeling of the IFNG promoter [71]. Extending these findings, recent data suggest that a broader epigenetic remodeling of the IFNG locus may be the basis for the enhanced IFNγ production of memory NK cells (C Romagnani, personal communication). Therefore, similar to what has been found for memory T cells [113,114], a global epigenetic reprogramming may also be responsible for the generation of memory NK cells [115]. However, in the current situation, it is very difficult to judge how much memory NK cells can contribute to immune responses against secondary infections with the same pathogen.

Concluding remarks

Some 45 years after the first description of "natural cytotoxicity", we already know a lot about NK cells, their important contribution to early and effective immune responses and how their effector functions are regulated through different surface receptors and cytokines. However, we now know that processes, such as education, differentiation and finally also the formation of a memory pool, additionally impacts on the activity of NK cells. Uncovering the molecular details of these processes will greatly enhance our understanding of these important immune cells and will pave the way for more effective NK cell-based therapies.

Abbreviations

ADCC, antibody-dependent cellular cytotoxicity; CMV, cytomegalovirus; DTH, delayed-type-hypersensitivity; IFN, interferon; IL, interleukin; ITIM, immunoreceptor tyrosine-based inhibitory motif; KIR, killer cell immunoglobulin-like receptor; MHC, major histocompatibility complex; NK, natural killer; RAG, recombination activating gene.

Disclosures

The authors declare that they have no disclosures.

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