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Non-cytotoxic functions of natural killer cells: direct pathogen restriction and assistance to adaptive immunity[1]

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Abstract

Natural killer (NK) cells were named after their ability to mediate spontaneous cytotoxicity during innate immune responses. However, it has become clear in recent years that they play an equally important role in restricting infections and assisting the development of adaptive immune responses via their ability to produce cytokines. In humans, a dedicated NK cell subset primarily fulfills these later functions. In this review we discuss the non-cytotoxic effector functions of NK cells and how they could be harnessed for immunotherapy and vaccine development.

Introduction

Natural Killer (NK) cells have been named for their ability to mediate spontaneous cytotoxicity against transformed and infected cells. However, in recent years it has become evident that their functions reach far beyond this traditional role. Notably, NK cells can assist in T cell polarization, dendritic cell maturation and innate immune control of viral infection by their ability to secrete immunomodulatory and antiviral cytokines. In this review, we will first briefly discuss the nature of the cytokine secreting NK cell subsets, their trafficking, and their tissue distribution. Next we will address the question of how particular NK cell functions are activated and which cell types in which tissue environments are able to provide NK cell-activating signals. Then, we will highlight recent data from in vitro and in vivo studies demonstrating the essential role of non-cytotoxic functions of NK cell responses in infections. Finally, we will explore future directions of research as well as how these non-cytotoxic functions could be harnessed for immunotherapy.

NK cell subsets in mouse and man

Natural killer (NK) cells were originally described as a homogenous population of innate lymphocytes characterized by their ability to spontaneously kill target cells (1-3). However, already in the 1980s, it was proposed that human NK cells in peripheral blood can be divided into at least two subsets based on the expression of CD56 and CD16 (Table 1) (4).The major

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subset of $CD56^{dim}CD16^{+}$ NK cells constitutes around 90 % of total blood NK cells, kills target cells upon proper recognition and secretes only low levels of IFN-γ (5). In contrast, $CD56^{bright}CD16^{-}$ NK cells (<10% of total blood NK cells) produce large amounts of cytokines including IFN-γ, TNF and GM-CSF upon stimulation by pro-inflammatory cytokines, but acquire cytotoxicity only after prolonged activation. Further differences between the subsets have also been found with respect to expression of inhibitory and activating receptors. While $CD56^{bright}CD16^{-}$ NK cells express high levels of the inhibitory CD94/NKG2A complex recognizing HLA-E, they do not express MHC class I allele-specific killer-inhibitory receptors (KIRs) that are in contrast expressed by $CD56^{dim}CD16^{+}$ NK cells. Regarding the expression of activating receptors, both NK cell subsets in human peripheral blood express the activating receptors NKG2D and NKp30 as well as NKp46, whose ligands are induced in pathogen-infected or stressed cells, yet a major discrepancy between the two subsets is the expression of antibody dependent cellular cytotoxicity (ADCC) mediating CD16 (FcγRIII) in the $CD56^{dim}$ subset (6,7). Finally, NK cell subsets also differ in the expression of chemokine receptors. Cytotoxic $CD56^{dim}CD16^{+}$ NK cells express CXCR1 and CX3CR1 and respond to IL-8 and fractalkine, the respective ligands for these receptors (8). Interestingly, only $CD56^{bright}$ NK cells express secondary lymphoid organ (SLO) homing markers such as CCR7, CD62L, and CXCR3, resulting in an enrichment of this subset in SLO and sites of inflammation, respectively (8-10). The question of whether or not the development of the human subsets is interconnected has been under investigation for some time. Recently, a number of studies suggested that $CD56^{bright}CD16^{-}$ NK cells are able to differentiate into $CD56^{dim}CD16^{+}$ NK cells upon prolonged activation (11,12).

Murine NK cells share a lot of the properties of human NK cells, but since they do not express the mouse homologue of CD56, it has proven difficult to identify functionally different NK cell subsets in mice. More recently however, three studies showed the presence of functionally different NK cell subsets in mice (Table 1) (13-15). The first study suggested differentiating mature NK cells according to their expression of CD27 into $Mac1^{high}CD27^{+}$ and $Mac1^{high}CD27^{-}$ subsets (13). Although these two subsets differ in the expression of inhibitory and activating receptors as well as chemokine receptors, there are striking differences between human and mouse subsets. Most importantly, $Mac1^{high}CD27^{+}$ NK cells are superior to $Mac1^{high}CD27^{-}$ ones in both the production of cytokines as well as cytotoxicity, whereas in human NK cell subsets $CD56^{bright}CD16^{-}$ NK cells are superior in IFN-γ production, but are not cytotoxic. In a second study, a new developmental pathway for a distinct NK cell subset was described in the thymus (14). These cells are characterized by expression of the IL-7 receptor, CD127, and the transcription factor GATA-3. Interestingly, this subset resembles human $CD56^{bright}CD16^{-}$ NK cells in expression of CD127, lower expression of inhibitory molecules and cytotoxic molecules, yet higher cytokine production after IL-12 stimulation. Furthermore, this subset seems to be enriched in lymph nodes compared to other NK cells although to a lesser degree compared to humans (15−30 % vs. 75 %, respectively) (10,14). It remains unclear so far which functions this NK cell subset has is in vivo, and how closely its development reflects $CD56^{bright}CD16^{-}$ NK cell generation in humans, given the previously discussed experimental evidence for a linear instead of a separate development of the two functionally diverse NK cell subsets in humans. In the third study, $NK1.1^{+}B220^{+}CD11c^{+}$ NK cells were found to be enriched in secondary lymphoid tissues and to secrete higher levels of IFN-γ compared to other mouse NK cells (15). However, NK cells of this subset also killed classical NK cell targets efficiently (16), and CD11c, B220 and MHC class II were upregulated on NK1.1 cells upon activation (17). Thus, $NK1.1^{+}B220^{+}CD11c^{+}$ cells might represent in vivo activated NK cells rather than the mouse equivalent of human $CD56^{bright}CD16^{-}$ NK cells. Nevertheless, the discovery of functionally different NK cell subsets in humans and mice has extended the field of NK cell research tremendously and yielded insight into important noncytotoxic functions of NK cells.

Tissue distribution and trafficking of NK cells

In line with their role in innate immunity and immune surveillance, NK cells are widely distributed in mammals, yet, intriguingly, the distribution of NK cell subsets differs between distinct anatomical sites, suggesting a specialization of NK cells subsets (3,18-20). In humans, the $CD56^{bright}CD16^{-}$ subset is markedly enriched in SLO, making up to 75 % of NK cells in lymph nodes and 50 % in the spleen (10). As lymph nodes are suggested to harbor 40% of all human lymphocytes, whereas probably only 2% of all lymphocyte circulate through peripheral blood at any given moment, $CD56^{bright}CD16^{-}$ NK cells in SLO constitute a remarkable pool of innate effector cells in humans. In mice, the distribution of NK cells subsets is also different as $Mac1^{+}CD27^{high}$, $CD127^{+}$ and $B220^{+}CD11c^{+}$ NK cells are all enriched in lymph nodes, whereas they represent minor subsets in spleen and peripheral blood (13,14). In general, while mouse NK cells are mainly excluded from B and T cell areas in both spleen and lymph nodes in the steady state, human NK cells are present at significant levels of 1−5% of all mononuclear lymph node cells in perifollicular T cell zones in these secondary lymphoid organs (Table 1) (9,18,19). Their localization in perifollicular regions in lymphoid organs potentially positions them to interact with incoming DCs that arrive through the afferent lymph. Notably, in human lymph nodes NK cells can be found in close proximity to resident DCs, furthermore intra-vital microscopy of mice revealed that NK cells were crawling and communicating with their environment in lymph nodes, forming contacts with DCs (18,21,22). But, NK cells can not only be found in lymphoid tissues, also lung, liver and skin have been shown to harbor significant numbers of NK cells in both mice and humans. Furthermore, a particular subset of NK cells is found in the placenta where it regulates specific developmental processes at the fetal-maternal interface (23,24). Uterine NK cells have been described to be less cytotoxic (25), but remodel decidual vessels as well as promote decidual cellularity (26). Placental remodeling by this NK cell subset seems to depend on their ability to produce IFN-γ. In addition, decidual NK cells produce other immunomodulatory factors, like galectin-1 and progestagen-associated protein 14 (27). Thus, NK cells seem to promote placenta development and create a tolerogenic environment for fetal semiallograft acceptance. Finally, NK cell distribution is not static as NK cells can recirculate between organs in a subset-specific manner (19). In addition to their distribution and recirculation in the steady state, NK cells are recruited to sites of inflammation (3). Detailed analysis of mouse NK cells showed that they can be recruited to lymph nodes, lung, liver, and central nervous system during infections. These NK cells apparently mainly originate from the spleen and the bone marrow as NK cells numbers decrease in these organs as they increase in other organs (28). Due to their expression of chemokine receptors such as CCR2, CCR5, CXCR3, and CX_3CR1, NK cells are able to respond to a large array of inflammatory cytokines (19,29). As discussed above, NK cell subsets in both man and mouse differ in the expression of certain chemokine receptors. Notably, in humans mainly $CD56^{bright}CD16^{-}$ and only few $CD56^{dim}CD16^{+}$ NK cells were found in a number of inflammatory sites suggesting that the $CD56^{bright}CD16^{-}$ NK cell subset is specifically recruited to sites of infection, inflammation and tumorigenesis (30-32). Finally, inflammation also causes a redistribution of mouse NK cells in spleen and lymph nodes into T cell zones into close proximity of DCs (21). The CXCR3-dependent recruitment to the lymph node in the mouse might be very different from the situation in humans as human $CD56^{bright}CD16^{-}$ NK cells express the lymph node-homing molecule CCR7 and are found in significant numbers also in non-inflamed lymph nodes (9,10,33). Additionally, separate NK cell development to $CD56^{bright}CD16^{-}$ NK cells in lymph nodes also contributes to the enrichment of this NK cell subset at these sites (34). Furthermore, in the non-inflamed human spleen, NK cells are found in close proximity to DCs in T cell zones, again demonstrating species-specific differences (18). Altogether the analysis of the distribution and localization as well as the recruitment of NK cells and more recently of NK cell subsets in mouse and man has provided important insight into NK cell biology, highlighted differences between the species and led to the discovery of new functions of NK cell subsets.

Activation of NK cells during innate immune responses

Initially, NK cells were recognized for their ability to mediate spontaneous cytotoxicity against target cell lines. Of particular interest, immune surveillance of B cell lymphomas that arise spontaneously in mice with a deficiency in β2-microglobulin, a component of MHC class I molecules, has been connected to NK cells and was dependent on the cytotoxic molecule perforin (35). Furthermore, natural cytotoxicity negatively correlated with tumor incidence in a 11-year follow-up study in humans (36). However, in addition to the important role for NK cells in innate immune surveillance by natural cytotoxicity, it was later discovered that additional signals were needed for NK cells to become fully activated. Numerous studies in humans and mouse models both in vivo and in vitro found that these signals can be provided by dendritic cells (37-42). The activation of NK cells was demonstrated to be mediated directly by cell-cell contact and indirectly via the secretion of cytokines such as type I interferons or monokines such as IL-12, IL-15, and IL-18. Among the soluble factors, IL-12 has been repeatedly observed to induce IFN-γ secretion and proliferation and was thought to be the most pivotal signal enhancing factor for NK cell effector functions in humans and in mice (18, 42-45). Yet, a recent study suggests that IL-15 acts as an even earlier and more crucial regulator of NK cell differentiation and function at least in mice (46). After in vivo stimulation with TLR ligands or bacterial and viral infection, it was shown that myeloid $CD11c^{high}$ DCs need to prime NK cells via presentation of IL-15 to produce IFN-γ and become cytotoxic against a MHC class I low cell line expressing NKG2D ligands. Curiously in analogy to adaptive T cell responses, NK cells needed to enter the draining lymph node to receive the priming signal to subsequently perform effector functions in the periphery. In humans, we have recently shown that IL-15 receptor alpha colocalizes at the synapse between DCs and NK cells and contributes to NK cell survival (47). Closer characterization of this synapse revealed that both activating signals such as mediated by IL-15 and inhibitory signals such as interactions of CD94/NKG2A and KIRs with MHC class I molecules are transmitted in spatially separated domains within the center of this synapse. The regulatory DC/NK cell synapse was formed very rapidly (1 −5min), lasted for long time periods (≥10min) and was distinct from activating NK cell synapses formed with classical MHC class I^{low} NK cell targets (48,49). Strikingly, DCs are protected from NK cell killing, although intracellular Ca^{2+} levels rise in NK cells upon interaction which have been correlated with killing of target cells (47,49). Notably, at later timepoints (>20 min) DCs seem to polarize preformed vesicles of IL12 to the synapse providing further activation signals to conjugated NK cells (50). These studies suggest that efficient NK cell activation and maintenance requires synapse formation with DCs.

Based on previous studies the different NK cell activating cytokines were believed to mediate different aspects of DC-induced NK cell stimulation and steer the innate immune response to distinct NK cell effector functions. While type I interferons, mainly secreted by plasmacytoid but also myeloid DCs are predominantly involved in the upregulation of NK cell-mediated cytotoxicity, IL-12 and IL-18 were found to influence IFN-γ production by NK cells (43,44, 51-53). Finally, in vitro studies suggest that another pathway for the activation / coactivation of NK cells might be the direct recognition of microbial products via TLRs or of infected cells via NKG2D/NCRs (54-59). These distinct pathways of NK cell activation might converge to regulate and activate different arms of NK cell effector functions, and thereby tailor the NK cell response to the needs of the particular immune response.

Direct antiviral functions of NK cells

As previously discussed, NK cells are readily recruited and activated at sites of viral infections. Traditionally, NK cells have been recognized for their protective role by directly killing infected cells. However, it is now established that cytokines such as IFN-γ and TNF-α, produced by NK cells, contribute to the control of multiple murine and human infections (Figure 1)(60). The effects of IFN-γ in innate immunity are manifold, ranging from

strengthening intrinsic immunity via the induction of antiviral factors or degradative pathways in exposed cells, to the activation of other innate lymphocytes such as macrophages. Since these functions have been more comprehensively summarized elsewhere (61,62), we will focus on the role of IFN-γ during herpesvirus specific immune control, in which NK cells play a crucial role. In MCMV infection, it was shown that DC-activated NK cells produce IFN-γ that is directly responsible to control viral infection (51,63). Moreover, it was demonstrated that NK cells can protect the host via secretion of IFN-γ, but not as efficiently as in combination with cytotoxicity (64). IFN-γ directly inhibits replication of MCMV, protecting against virus-induced pathogenesis and lethality (65,66). In addition, IFN-γ is also critical for efficient clearance of persistent viral replication and suppresses MCMV reactivation from latency (65). Notably, IFN-γ inhibits growth of MCMV in infected macrophages in a cell-type specific manner via suppression of immediate early protein 1 expression (67). With respect to human herpesviruses, there is evidence to support the role of NK cells in limiting the early infection of HCMV, a β-herpesvirus, but also of Epstein Barr virus (EBV), a γ-herpesvirus, using cytotoxic and non-cytotoxic functions (45,68,69). In the case of EBV, we demonstrated recently that $CD56^{bright}CD16^{-}$ NK cells curb B cell transformation by EBV upon activation by DCs via IFN-γ by a yet unknown mechanism, presumably involving down regulation of the viral oncogene LMP1 (45). NK cells from tonsils, the site of primary EBV infection, were particular effective due to their ability to produce higher amounts of IFN-γ that their counterparts from blood. Interestingly, as NK cells are also recruited to sites of inflammation and tumorigenesis, it is noteworthy that the infiltrating NK cells in a number of human inflammatory lesions were found to be mainly $CD56^{bright}CD16^{-}$ NK cells, although $CD56^{dim}CD16^{+}$ express chemokine receptors such as CXCR1, CX3CR1 and ChemR23 that could also guide them to these sites (31,32). The homing cells were negative for perforin and had an increased capability to produce IFN-γ upon stimulation with a combination of IL-12 and IL-18. Thus, NK cells can limit herpesvirus latency and restrict reactivation of lytic infection by these viruses by directly suppressing herpesviral gene expression via IFN-γ. In a broader context it demonstrates that the role of NK cells goes beyond traditional cytotoxic functions and that cytokines, in particular IFN-γ, secreted by NK cells are important effector molecules that contribute directly to pathogen control.

Immunomodulatory functions of NK cells

In addition to their direct antiviral role, a number of recent studies illustrated additional roles for NK cells in the modulation of innate immunity and polarization of adaptive immunity, extending the influence of NK cells into adaptive immunity.

Maturation of DCs by NK cells—DC maturation supplies a signal that links innate immunity to adaptive immune responses. Previously, we discussed activation of NK cells by mature DCs, yet, activated NK cells can also trigger DC maturation (Figure 1). DC maturation has been reported after NK cell recognition of MHC Class I^{low} tumor cells and NK cell activation with IL-2 (39,40,70,71). NK cells mature DCs via TNF-α and IFN-γ production, and additional cell-to-cell contact-dependent signals. The superior ability of NK cells to recognize virus infected or transformed cells via NKp46 and NKG2D, especially after virus-induced MHC class I down-regulation, might make NK cells important accessory cells for DC-initiated immune responses (72). NK cell-matured DCs display up-regulation of CD86 and secrete IL-12 (39,40). Because DC maturation might be confined to the site of innate lymphocyte activation, it is potentially a local and very early event. However, this interaction in turn expands and activates innate lymphocytes and initiates T cell immunity. Indeed, the interplay between DCs and NK cells can completely replace $CD4^{+}$ T cell help in the induction of an anti-tumor $CD8^{+}$ response (70). Together, these findings demonstrate that cross-talk between NK cells and DCs is important during innate immunity, influencing the activation status of both cell types potentially amplifying immune activation.

T cell polarization by NK cells—To successfully control infection, adaptive immune responses need to be tailored to the respective pathogen. Polarization of T cell responses is mediated by DCs in the initial priming phase and takes largely place in secondary lymphoid organs (73). As previously discussed, human secondary lymphoid organs harbor mainly $CD56^{bright}CD16^{-}$ NK cells, which are the NK cell subset primarily activated by DCs. Furthermore, studies have shown both in vitro and in vivo that NK cells are located in lymph nodes in close proximity to DCs. Intravital microscopy revealed that NK cells were highly motile in lymph nodes in steady-state sampling their microenvironment and forming aggregates with DCs and B cells (21,22). Upon inflammation, NK cells are recruited to lymph nodes and importantly, upon infection with *Leishmania major*, IFN-γ-secreting NK cells were found to contact the same DC as antigen-specific $CD4^{+}$ T cells in the lymph node (21). This observation provides insight into the regulation of T cell responses by NK cells as it has been demonstrated that upon activation by mature DCs, NK cells produce high levels of IFN-γ that are sufficient to mediate Th1 polarization in mouse models and human allogeneic immune responses (Figure 1) (21,33,74,75). Although there are clear parallels between mice and humans, important details of NK cell-assisted T cell polarization appear to be different. In humans, tissue-resident NK cells from human secondary lymphoid tissues supported Th1 polarization more efficiently than blood NK cells by their superior ability to produce IFN-γ after stimulation with DCs (75). Yet in mice, NK cells need to be recruited to lymph nodes in a CCR7-independent, CXCR3-dependent manner to support T cell polarization (33). Shaping of immune responses by NK cells is particular important for a variety of immune responses, since Th1 polarized T cell responses have been found to be more effective in the immune control of tumors and viral infections in mice (76,77). Furthermore, Th1-based immune control has been correlated with protection from HCMV after primary infection in kidney transplant patients (78).

NK cells in immunotherapy

Immunological research is driven partly by an interest in the basic biology of the immune system, but even more by an interest into translating research into the clinic and vaccine development. A number of clinical studies have attempted to take advantage of the cytotoxic abilities of NK cells, but very little attempts have been made to include NK cells to modulate and direct immune responses via secretion of cytokines (79-82). Yet, there is evidence that targeting of NK cells directly or indirectly via DCs can polarize T cell responses during vaccination. In mice, a number of adjuvants such as the TLR7/8 antagonist R848 or the microbial product-containing emulsion Ribi were shown to polarize Th1 responses via indirect activation of NK cells that provide IFN-γ necessary for efficient T cell priming by DCs in lymph nodes (33). In contrast, other adjuvants such as the TLR9 antagonist CpG1826 or complete Freund's adjuvant that did not lead to NK recruitment did not achieve Th1 polarization in this model. Another commonly used adjuvant, the TLR3/mda-5 ligand polyI:C, induces strong Th1 responses and has been shown to directly induce IFN-γ production in NK cells. Accessory cells such as DCs or monocytes could amplify IFN-γ production by secretion of IL-12 or IL-18 (18,57,83). In our hands the stimulation of human monocyte-derived DCs with different adjuvants resulted in striking differences in the ability of DCs to induce NK cell activation (45). PolyI:C induced the highest secretion of IL-12 and led to strong upregulation of IL-15Rα expression, inducing IFN-γ production and proliferation of mainly the $CD56^{bright}CD16^{-}$ NK cell subset. In addition, we also showed that $CD56^{bright}CD16^{-}$ NK cells from secondary lymphoid organs but not from peripheral blood produced sufficient IFN-γ after stimulation by polyI:C-matured DCs to polarize human allogeneic T cell responses (75). Hence, we propose that NK cells should be harnessed for immunotherapy not only because of their potential antitumor functions, but also for their ability to mobilize and polarize adaptive immune responses via DCs. Adjuvants should not only be assessed for their ability to directly stimulate DCs, but also for their ability to directly or indirectly stimulate NK cells to support

the development of Th1 responses, which are desired in a majority of cancer immune therapy or vaccine development approaches.

Conclusions

In the recent years, studies have provided new insights into the versatile functions of NK cells in viral, bacterial, and parasite infections, as well as anti-tumor immunity. Most importantly, the classical view of NK cells as spontaneous cytotoxic cells has been extended and additional NK cell functions are now appreciated. In particular, cytokines secreted by activated NK cells during innate immune responses have gained much attention. IFN-γ, secreted by NK cells, was found to be important not only in minimizing the spread of infections, but, it also polarizes adaptive immunity to efficiently protect the host. Furthermore, additional studies in mouse and human have documented that DC/NK cell interactions take place both at peripheral inflamed sites and in secondary lymphoid tissues, and that these interactions are crucial for optimal reciprocal activation of these two innate lymphocyte subsets. The difference between the two species with respect to this interaction, however, seems to be that humans constitutively harbor a substantial amount of NK cells in secondary lymphoid tissues, which are enriched in the NK cell subset that preferentially responds to DC activation. In contrast, NK cells are rare in murine secondary lymphoid tissues, but get recruited to these sites upon mature DC migration into secondary lymphoid organs. In summary, these results suggest that NK cell activation by DCs and its polarizing effect on adaptive immune responses is important in a number of infection models and should be harnessed for vaccine development by choosing adjuvants that enable DCs to activate NK cells and to prime preferentially Th1-polarized immune responses.

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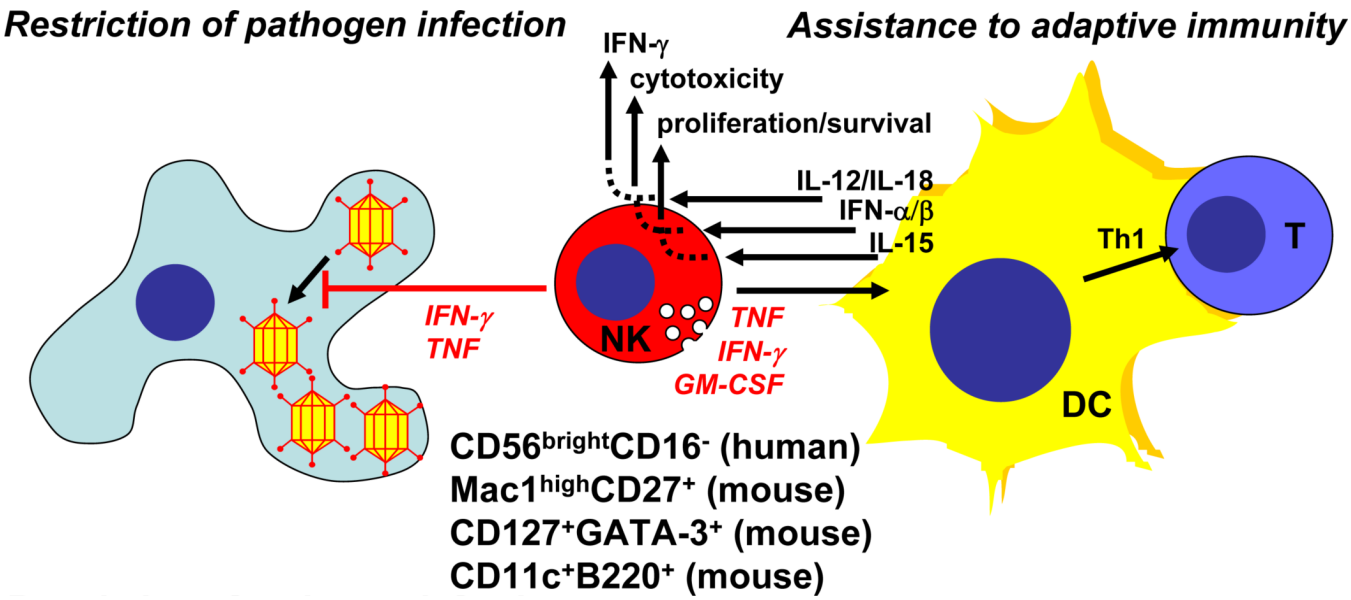

Figure 1.

Biological functions of non-cytotoxic NK cells. $CD56^{bright}CD16^{-}$ human NK cells and possibly their mouse counterparts ($Mac1^{high}CD27^{+}$ and/or $CD127^{+}GATA\text{-}3^{+}$) restrict pathogen infections primarily by IFN-γ secretion (left side). In addition, they mature and polarize DCs for more efficient priming of Th1 cells. These mature DCs can further augment NK cell responses via IL-12/IL-18 (IFN-γ secretion by NK cells), IFN-α/β (NK cell cytotoxicity) and IL-15 (NK cell proliferation/survival), and stimulate mainly the $CD56^{bright}CD16^{-}$ NK cell subset enriched in secondary lymphoid tissues.

Table 1

Some differences between mouse and human NK cells

Affected aspect	Mouse		Human		References
Receptor/ligand interactions					
Natural cytotoxicity receptors (NCRs)	NKp46		NKp30, p44, p46		(7)
Ligands for the activating NK cell receptor NKG2D	Rae1α—ε, H60, MULT-1		MICA/B, ULBP1−4, RAET1G		(84)
Inhibitory receptors for MHC class Ia molecules	Ly49		KIRs		(85)
Distribution and subsets					
NK cell frequency in lymph nodes	0.1−0.3%[1]		1−5%[1]		(9,10,21,33,74)
NK cell subsets enriched in	**SLO**[2]	**blood**	**SLO**[2]	**blood**	
NK cell subset markers (cytotoxicity/ cytokine secretion)	$Mac1^{high}$ $CD27^{+}$ (high/high) $CD127^{+}$ $GATA\text{-}3^{+}$ (low/high) $CD11c^{+}$ $B220^{+}$ (high/high)	$Mac1^{high}$ $CD27^{-}$ (low/low) $CD127^{-}$ $GATA\text{-}3^{-}$ (high/low) $CD11c^{-}$ $B220^{-}$ (low/low)	$CD56^{bright}$ $CD16^{-}$ (low/high)	$CD56^{dim}$ $CD16^{+}$ (high/low)	(5,13-15,20)

[1] Percentage of mononuclear cells is listed.

[2] Secondary lymphoid organs is abbreviated SLO.