REVIEW

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Functions of natural killer cells

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Natural killer (NK) cells are effector lymphocytes of the innate immune system that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage. Recent research highlights the fact that NK cells are also regulatory cells engaged in reciprocal interactions with dendritic cells, macrophages, T cells and endothelial cells. NK cells can thus limit or exacerbate immune responses. Although NK cells might appear to be redundant in several conditions of immune challenge in humans, NK cell manipulation seems to hold promise in efforts to improve hematopoietic and solid organ transplantation, promote antitumor immunotherapy and control inflammatory and autoimmune disorders.

NK cells were originally described as large granular lymphocytes with natural cytotoxicity against tumor cells. NK cells were later recognized as a separate lymphocyte lineage, with both cytotoxicity and cytokine-producing effector functions[1]. The acquisition of cell cytotoxicity during evolution has been associated with the development of highly sophisticated and robust mechanisms that control the initiation of the cytolytic processes and avoid tissue damage. Along this line, much progress has been made over the last fifteen years in the dissection of the mechanisms that allow NK cells to discriminate target cells from other healthy 'self' cells. These data have been instrumental in defining several recognition strategies and in the emergence of the 'dynamic equilibrium concept'. The NK cell detection system includes a variety of cell surface activating and inhibitory receptors, the engagement of which regulates NK cell activities. Thus, the integration of antagonistic pathways upon interaction with neighboring cells governs the dynamic equilibrium regulating NK cell activation and dictates whether or not NK cells are activated to kill target cells[2].

Activating NK cell receptors detect the presence of ligands on cells in 'distress', such as the stress-induced self ligands recognized by NKG2D (human ULBP and MIC molecules, as well as mouse RAE1, H60 and MULT1 molecules)[3] (**Fig. 1**). Other alert molecules include infectious nonself ligands (for example, the cytomegalovirus-encoded m157 recognized by Ly49H in the mouse) and Toll-like receptor (TLR) ligands. Indeed, NK cells express several TLRs[4]. *In vitro* exposure of NK cells to TLR ligands induces interferon (IFN)-γ production and enhances cytotoxicity. However, this process is more efficient when accessory cells are present in the environment of NK cells, suggesting that the role of TLRs in NK cells might be indirect *in vivo*[5,6]. NK cells also express the low-affinity Fc receptor CD16, enabling them to detect antibody-coated target cells and to exert antibody-dependent cell cytotoxicity (ADCC).

NK cells use inhibitory receptors to gauge the absence of constitutively expressed self molecules on susceptible target cells. In particular, NK cells express MHC class I–specific receptors and 'lose' inhibitory signals when encountering MHC class I–deficient hematopoietic cells in several *in vitro* and *in vivo* models[7,8]. As a consequence, NK cells have been described as able to recognize 'missing self' on hematopoietic cells[9]. The MHC class I–specific inhibitory receptors include the killer cell immunoglobulin-like receptors (KIRs) in humans, the lectin-like Ly49 dimers in the mouse and the lectin-like CD94-NKG2A heterodimers in both species[7,8] (**Fig. 1**). A conserved feature of these inhibitory receptors resides in the presence of one or two intracytoplasmic inhibitory signaling domains called immunoreceptor tyrosine-based inhibition motifs (ITIMs)[2]. By interacting with MHC class I molecules that are constitutively expressed by most healthy cells in steady-state conditions but that may be lost upon stress, inhibitory MHC class I receptors provide a way for NK cells to ensure tolerance to self while allowing toxicity toward stressed cells. MHC class I is not the only constitutive self signal detected by NK cells, as other inhibitory receptors (for example, mouse NKR-P1B, human NKR-P1A and mouse 2B4) that recognize non-MHC self molecules (for example, Clr-b, LLT-1 and CD48, respectively) also regulate NK cell activation[10].

NK cell anatomical localization

Consistent with their function as innate sentinels, NK cells are widespread throughout lymphoid and nonlymphoid tissues. In most tissues, NK cells represent a minor fraction of total lymphocytes (from 2% in mouse spleen to 10% in mouse lung and from 2% to 18% in human peripheral blood)[11]. Human NK cell turnover in blood is around 2 weeks[12], consistent with data in the mouse[13,14]. Distinct NK cell subsets have been defined in mice and humans based on phenotypic, functional and anatomical features.

In the mouse, three subsets of NK cells differing in expression of CD11b and CD27 have been described[15]. NK cell differentiate from $CD11b^{dull}CD27^{+}$ NK cells[16], by way of $CD11b^{+}CD27^{+}$ double-positive NK cells, to the most mature $CD11b^{+}CD27^{dull}$ NK cells. Double-

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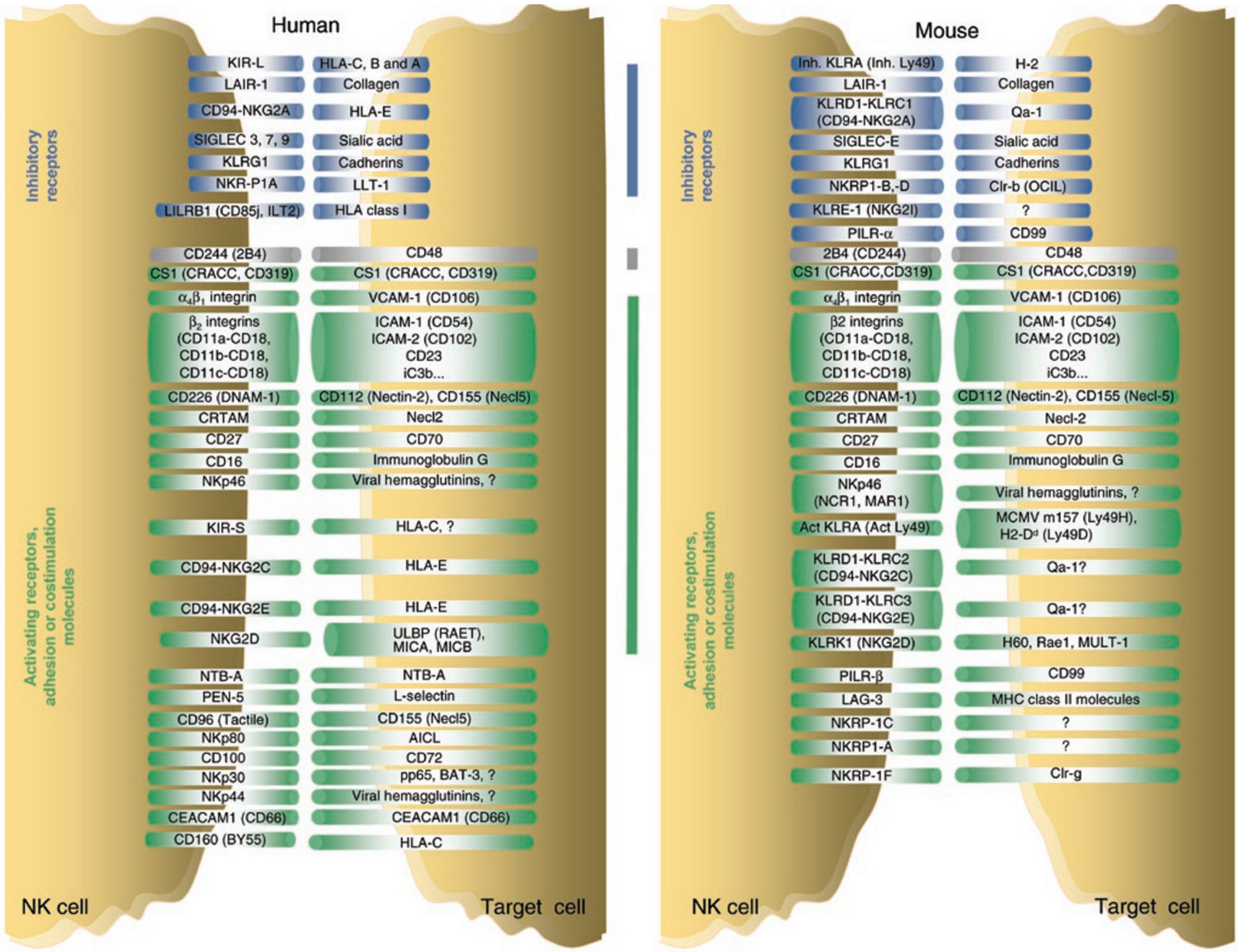

Figure 1 The NK cell–target cell 'zipper'. NK cell activation programs result from the integration of multiple activating and inhibitory signals that vary depending on the nature of the interacting cells. These signals involve ITAM (immunoreceptor tyrosine-based activation motif)-bearing molecules and other stimulatory receptors and adhesion molecules, as well as ITIM-bearing inhibitory receptors. Some human (left) and mouse (right) receptor-ligand interactions are depicted here, to illustrate the combinatorial nature of the NK cell interaction repertoire. Cytokines, chemokines and their receptors are not shown, but are also crucial for the regulation of NK cell functions. Inhibitory receptors are in blue; 2B4, which can act as an activating or an inhibitory molecule, is in gray; other receptors are in green. Vertical lines indicate the receptor-ligand pairs conserved between mice and humans, which consist either of real orthologs (for example, human and mouse NKp46) or examples of convergent evolution (for example, KIR and Ly49). KIR, killer immunoglobulin-like receptors; LIR, immunoglobulin-like transcript; LAIR, leukocyte-associated immunoglobulin-like receptor; SIGLEC, sialic acid binding immunoglobulin-like lectins; KLRG-1, killer cell lectin-like receptor G1; NKR-P1, NK cell receptor protein 1; HLA, human leukocyte antigen; LLT, lectin-like transcript; CRTAM, class I restricted T cell–associated molecule; Necl-2, nectin-like 2; Tactile (also known as CD96), T cell–activated increased late expression; CEACAM1, carcinoembryonic antigen–related cell adhesion molecule 1; PILR, paired immunoglobulin-like type 2 receptor; NTB-A, NK-T-B antigen; CRACC, CD2-like receptor-activating cytotoxic cell; VCAM-1, vascular cell adhesion molecule-1; ICAM, intercellular adhesion molecule; Ocil, osteoclast inhibitory lectin.

positive and CD11b^{+}CD27^{dull} NK cells show comparable capacities to kill target cells and to secrete IFN-γ in a broad range of *in vitro* stimulation conditions, but CD11b^{+}CD27^{dull} NK cells are in replicative senescence[15]. The three NK cell subsets differ widely in tissue distribution[15]: CD11b^{dull}CD27^{+} NK cells are predominantly found in bone marrow and lymph node, whereas CD11b^{+}CD27^{dull} NK cells are more abundant in blood, spleen, lung and liver, and double-positive NK cells are more homogeneously distributed.

In humans, NK cells can be divided into CD56^{dim} and CD56^{bright} NK cell subsets, which differ in their homing properties[17]. Around 90% of peripheral blood and spleen NK cells are CD56^{dim}CD16^{+} and express perforin. These CD56^{dim} NK cell are cytotoxic and produce IFN-γ upon interaction with tumor cells *in vitro*[18]. In contrast, most NK cells in lymph nodes and tonsils are CD56^{bright}CD16^{-} and lack perforin[19]. These cells readily produce cytokines such as IFN-γ in response to stimulation with interleukin (IL)-12, IL-15 and IL-18 (ref. 17). The lack of CD56 expression on mouse NK cells, combined with the difference in CD27 and CD11b expression on human versus mouse NK cells, blurs attempts to define a direct correspondence between NK cell subsets in human and mice. Nevertheless, a range of observations suggests a possible similarity between CD56^{bright} human NK cells and CD11^{dull} mouse NK cells: their anatomical localization (for example, enrichment in lymph nodes versus paucity in spleen, peripheral blood and lungs), phenotype (for example, lack of cell surface KIR or Ly49, low intracytoplasmic perforin content, cell surface expression of IL-7R and c-kit) and elevated proliferative potential. Along this line, the role of lymph nodes and other secondary lymphoid organs, such as tonsils, in NK cell biology is emerging. In these tissues, NK cells are phenotypically and functionally very distinct from circulating and splenic NK cells, and several studies suggest that they may be sites of NK cell production and maturation in mice and humans[19,20].

Three types of cell surface receptors are involved in NK cell traffic in the mouse (**Fig. 2**). The chemokine receptors CCR2, CCR5, CXCR3 and CX3CR1 regulate NK cell recruitment upon inflammation[11]. NK cell entry to lymph nodes from blood is dependent on CD62L (ref. 21). A sphingosine 1-phosphate (S1P) receptor, $S1P_5$, is also involved in NK cell homing. Within lymphocytes, $S1P_5$ is selectively expressed on NK cells and is acquired with maturation in both humans and mice[22]. $S1P_5$-deficient mouse NK cells accumulate in bone marrow and lymph nodes and are depleted from blood, spleen and lung. In humans, CCR7 is expressed on $CD56^{bright}$ NK cells and is likely to regulate their homing to lymph nodes[23]. In addition, CXCR1 and ChemR, which are expressed on the $CD56^{dim}$ human NK cell subset, are likely to play a role during recruitment of NK cells into peripheral inflammatory sites[24].

Regulation of NK cell functions

The intensity and the quality of NK cell cytotoxic and cytokine responses depend on the cytokine microenvironment, as well as on interactions with other cells of the immune system, such as T cells, dendritic cells (DCs) and macrophages[25]. Type I IFN, IL-12, IL-18 and IL-15 are potent activators of NK cell effector function[26]. It is also well known that IL-2 promotes NK cell proliferation, cytotoxicity and, to some extent, cytokine secretion[1]. In humans, the lymph nodes, where $CD4^+$ T cells and NK cells interact, might be the location where T cell–derived IL-2 boosts NK cells[27]. In the mouse, $CD8^+$ T cells can provide help to NK cells when both cell types infiltrate tumors, but the molecular mechanisms of this interaction remain to be elucidated[28]. NK cell function can be regulated by transforming growth factor (TGF)-β[29], and by regulatory T cells through a TGF-β-dependent mechanism in human and mice[30,31]. Although NK-T cell cooperation thus seems to be an important factor influencing NK cell activation, NK cells from T cell–deficient mice (for example, RAG-deficient mice) appear normal and are currently successfully used as a source of NK cells in many experimental settings.

It has only been recently appreciated that despite their name and original functional definition, a substantial fraction of NK cells isolated from human peripheral blood or mouse spleen are not killer cells[25]. In the mouse, resting splenic NK cells harbor a poor cytotoxic potential because of reduced expression of granzyme B and perforin, which are induced upon stimulation with cytokines or after infection with murine cytomegalovirus (MCMV)[32]. Similarly, resting human peripheral blood NK cells harbor poor effector function[33]. Like T cells, NK cells thus require 'priming' for full activation[25,34]. The molecules involved in NK cell priming include IL-15 in the mouse[34], but most NK cell priming mechanisms remain to be unveiled.

NK cells undergo a maturation step through the recognition of self molecules that are constitutively expressed in steady-state conditions. A prototypical example of this process is the MHC class I–induced NK cell 'education'. Ever since the original observation of the ability of NK cells to detect 'missing self' using their inhibitory receptors for self MHC class I, it has been known that NK cells follow an education process to become both competent to recognize 'missing self' and tolerant to self[35]. This education process requires the recognition of self–MHC class I molecules by cognate inhibitory receptors, such as Ly49 molecules in mice and KIRs in humans[18,36–39]. Altogether, it thus seems that several adaptive immune response components shape NK cell responses, emphasizing the plasticity and the adaptive nature of these innate immune cells.

NK cells and cancer

In vitro studies using cells from humans and several other mammalian species, as well as *in vivo* studies in mice and rats, have long suggested that tumor cells are recognized as NK cell targets[1]. The *in vivo* analyses relied on antibody-mediated depletion of NK cells in mice, targeting either NK1.1 or the glycolipid asialo-GM1. However NK cell depletion with antibodies to NK1.1 may also affect populations of invariant natural killer T cells and other $NK1.1^+$ T cell populations. The selectivity of NK cell depletion with asialo-GM1 antibodies has also been hampered by the expression of asialo-GM1 by several cell types including myeloid cells, epithelial cells and T cell subsets. Caution is therefore required when interpreting studies based upon antibody depletion because of the lack of specificity of antibody treatment against NK populations. Despite these key caveats, many independent studies advocate a role for NK cells in the control of tumor development in mice.

Mouse NK cells are involved in the *in vivo* rejection of several transplanted tumors, in a manner dependent upon the presence or absence of NK cell receptor ligands expressed by the tumor[40]. The lack of MHC class I expression (for example, on the classical RMA/S MHC class I–deficient mouse lymphoma cells[9]) or the upregulation of NKG2D ligands (for example, H60, Rae1β, Rae1δ, Rae1γ, Mult-1)[41,42] or of CD70, the CD27 ligand[43], can render tumor cells susceptible to NK cell–mediated lysis. In some of these experimental models, NK cell–mediated elimination of tumor cells induces the subsequent development of tumor-specific T cell responses to the parental tumor cells[41,43]. If it holds true in humans,

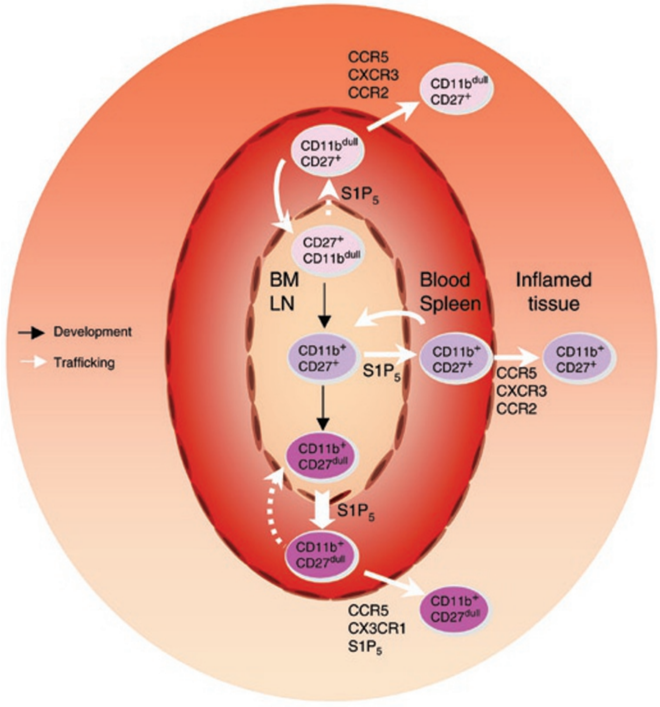

Figure 2 NK cell trafficking. A model of mouse NK cell trafficking is proposed in which NK cells develop in the bone marrow (BM, central circle). Recent evidence suggests that they can also arise in lymph nodes (LN). NK cells undergo a process of maturation (black arrows) through at least three discrete stages defined by the CD11b and CD27 markers (from $CD11b^{dull}CD27^+$ to $CD11b^+CD27^+$ and then to $CD11b^+CD27^{dull}$). In steady-state conditions, the presence of NK cells in bone marrow and lymph nodes is regulated in part by $S1P_5$, a G protein–coupled receptor acquired upon NK cell maturation. In inflammatory conditions, NK cells extravasate through endothelium by means of chemokine receptors, as indicated, that differ among subsets.

this very important result would enhance the appeal of NK cell–based immunotherapeutic approaches. A role for NK cells in tumor immunosurveillance has also been reported in models of spontaneous and induced tumors. Indeed, mice depleted of NK cells are more susceptible to methylcholanthrene-induced sarcomas, and, in this model, NK cells seem to use in part the NKG2D pathway to protect the host from tumor development[44]. NK cells have also been implicated in controlling the growth of B cell lymphomas that spontaneously arise in mice lacking both perforin and β_2-microglobulin[45]. In addition to their endogenous protective role in tumor models, NK cells are also mediators of the antitumor effects of several recombinant cytokines, such as IL-2, IL-12, IL-18 and IL-21 (ref. 40).

In humans, the paucity of NK cell–selective deficiencies[46] has hampered the characterization of NK cell biological function *in vivo* in general and in antitumor immunosurveillance in particular. However, an 11-year follow-up epidemiologic survey has shown that the extent of NK cell activity in peripheral blood is associated with cancer risk in adults: low NK cell activity is associated with increased cancer risk[47]. In selected human malignancies such as acute myeloid leukemia, allogeneic hematopoietic cell transplantations have shown that the development of donor NK cells in recipient tumor patients lacking donor KIR ligands can lead to improved engraftment and post-transplant survival, in the absence of graft-versus-host disease[48]. However, several aspects of these allogeneic transplantation settings must be further dissected, as attempts to replicate the beneficial role of a KIR-HLA donor-recipient 'mismatch' have failed in studies involving other malignancies and/or modifications to the original protocol (for example, conditioning regimen, dose and purity of $CD34^+$ donor cells)[49]. In an alternative approach, the blocking of NK cell MHC class I–specific inhibitory receptors increases NK cell effector function against tumor cells *in vivo* in mice[50], and this approach is currently being tested in phase 1 clinical trial in human acute myeloid leukemia. The manipulation of NK cell–mediated 'missing self' recognition is thus being harnessed to develop potentially promising antitumor strategies. These innovative NK cell–based therapeutic protocols complement the reappraisal of the role of NK cells in ADCC in the treatment of cancer[51]. Of importance, clinical-grade production of NK cells has proven efficient[52], and NK cell–mediated therapy after hematopoietic cell transplantation seems safe[53].

NK cells and viruses

Infection by many viruses, such as herpes simplex virus-1, influenza virus or the ectromelia poxvirus, can be controlled by NK cells in mice[54]. Yet the most compelling evidence for a role for NK cells in early defense against viruses were obtained in a study showing increased susceptibility or resistance to the herpesvirus MCMV after NK cell depletion or NK cell adoptive transfer, respectively. Defects in NK cell activity, such as decreased production of IFN-γ or cytotoxicity, also render mice more susceptible to MCMV infection[54,55]. NK cells control MCMV infection by various mechanisms, depending on the mouse strain analyzed. In C57/BL6 mice, NK cells selectively recognize MCMV-infected cells through the interaction between a CMV-encoded cell surface molecule, m157, and the activating NK cell receptor Ly49H (refs. 56,57). In MCMV-resistant Ly49H$^-$ mouse strains, other NK cell receptor-ligand pairs participate in the cognate recognition of MCMV-infected cells by NK cells. For instance, the Ly49P NK cell activating receptor is associated with virus resistance in Ma/My mice and interacts with H-2D^k molecules[58]. Whether an MCMV peptide is presented by H-2D^k to ensure Ly49P interaction is unknown. In addition, the secretion of type I interferon and IL-12 by plasmacytoid DCs increases NK cell proliferation, cytotoxicity and IFN-γ production[59], whereas chemokines such as CCL3 (MIP-1α), CXCL10 (IP-10) and CXCL9 (MIG) coordinately

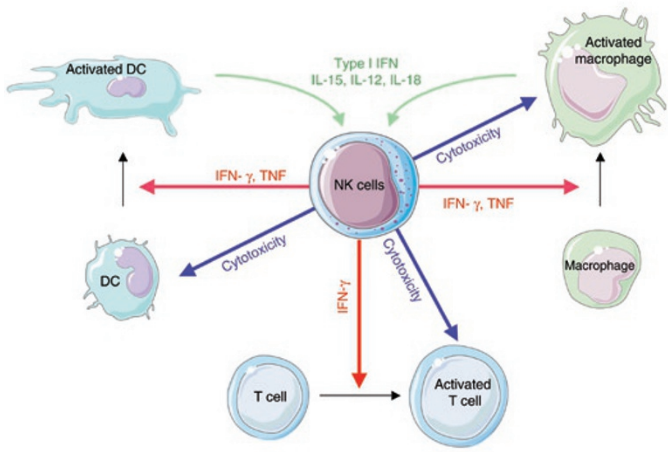

Figure 3 Regulation of immune responses by NK cells. Upon priming by various soluble factors (for example, IL-15, type I IFN, IL-12, IL-18), NK cells boost (red arrows) the maturation and activation of DCs, macrophages and T cells, through a combination of cell surface receptors and cytokines. Conversely, NK cells can also kill (blue arrows) immature DCs, activated $CD4^+$ T cells and hyperactivated macrophages. These NK cell regulatory functions are kept in check by the recognition of constitutively expressed self molecules (for example, MHC class Ia and MHC class Ib molecules) by means of inhibitory receptors (for example, human inhibitory KIR, mouse inhibitory Ly49 molecules, human and mouse CD94-NKG2A).

regulate NK cell trafficking[60]. The many MCMV genes involved in evasion of NK cell control also illustrate the importance of NK cells during MCMV infection. These mechanisms include the prevention of NK stimulation through downregulation of NKG2D ligands (for example, MCMV m145, m152, m155) and the expression of MCMV-encoded decoy ligands, including MHC class I homologs that inhibit NK cell function (for example, MCMV m144)[61]. In 129/J mice, m157 also plays a direct decoy role in MCMV evasion by interacting directly with the Ly49I inhibitory receptor, whose cognate ligands include H-2Kb molecules[57]. In the rat, a rat cytomegalovirus (RCMV) gene product (RCTL) closely resembles rat Clr-b (Ocil), a ligand for the inhibitory NK cell receptor NKR-P1B, and serves as an RCMV decoy[62]. The correlation between the downregulation of Clr-b expression on RCMV-infected cells and the control of RCTL-deficient RCMV infection by NK cells strongly supports the importance of 'missing-self' (Clr-b) recognition by NK cells in the control of a viral infection *in vivo*.

Only a few cases of selective NK cell deficiencies have been reported in humans, but most of these are consistent with a role for NK cells in defense against human herpesvirus infections[46]. Thus, the participation of mouse NK cells in the control of herpesviruses in experimental conditions seems to hold true in humans in a natural environment. However, half the patients with NK$^-$ severe combined immunodeficiency (*IL2RG* or *JAK3* deficiency) who undergo either allogeneic hematopoietic transplantation or *IL2RG* gene therapy have no or very few circulating NK cells for up to 30 years, yet they do not develop any detectable sensitivity to viruses (or tumors)[63]. Thus, one might ask whether NK cells perform a crucial function in humans. However, redundancy is one of the critical elements that ensure the robustness of immunity and of living beings in general. The possible adaptation of humans to the lack of NK cells does not prove that NK cells are useless. NK cells might play nonredundant functions in some disease conditions (such as microbial infections) that have disappeared or been rendered rare because of hygiene development. In addition, the clinical consequences of NK cell defects (for example, delay in the early control of microbial replication and/or in the arming of the immune response) might be exacerbated in the case of two or more simultaneous assaults on the immune system, during which immune cells might be overwhelmed. This situation of natural immune challenge might be unlikely to be encountered, because of health care, by patients with severe combined immunodeficiency. Thus, although the *in vivo* role of NK cells in humans is still a matter of debate, the biological consequences of NK cell responses should not be hastily underestimated.

Another important role for NK cells in regulating the extent of antiviral immune responses is now emerging: the control of immunopathology[64]. This role is seen in mice with encephalitis induced by Theiler's virus or myocarditis induced by coxsackie B3 virus infection[65,66]. In both models, NK cell depletion accelerates the development of these pathologies. Similarly, by controlling MCMV infection, mouse NK cells accelerate the initiation of $CD8^+$ T cell responses and dampen early, type I IFN–dependent immunopathology induced by uncontrolled virus dissemination[67]. Recent experiments conducted in granzyme-deficient mice have also shown a predominant role played by NK cells in the control of macrophage activation and the appearance of hemophagocytosis lymphohistiocytosis (HLH)-like syndromes[68]. In humans, HLH-like syndromes are rare and severe disorders characterized by abnormal proliferation and activation of well- differentiated macrophages or histiocytes[69]. In its inherited form, HLH is a pediatric disease caused by genetic mutations affecting proteins of the cytotoxic granule secretory pathway (**Supplementary Table 1** online)[69]. HLH may appear after a common viral infection and is characterized by fever, splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia and hemophagocytosis. HLH may also occur in adults (reactive HLH) as a complication of infections, lymphoma, cancers or autoimmune diseases, notably systemic lupus erythematosus or adult-onset Still's disease. Reactive HLH is most frequently coupled to reduced cell-mediated cytotoxicity[69]. The role of microbial infection in the onset of inherited HLH and reactive HLH is supported by experimental viral infection in mutant mice[68,70,71]. These data thus show that genetic and acquired deficiencies in cell-mediated cytotoxicity are often associated with HLH-like syndromes, which involve macrophage hyperactivation and develop upon microbial infections in human and mice. In addition to $CD8^+$ T cell cytotoxicity[70], NK cell cytotoxicity might represent a way of eliminating overstimulated macrophages[68] (**Fig. 3**). This hypothesis is consistent with the colocalization of NK cells and macrophages in the splenic red pulp, as well as in peripheral tissues[11], and with the *in vitro* cytotoxicity of human NK cells toward autologous macrophages, seen only if the latter are activated[72]. Thus, NK cells seem to reduce the risk of developing inflammatory disorders, both by controlling microbial infections and by eliminating activated cells.

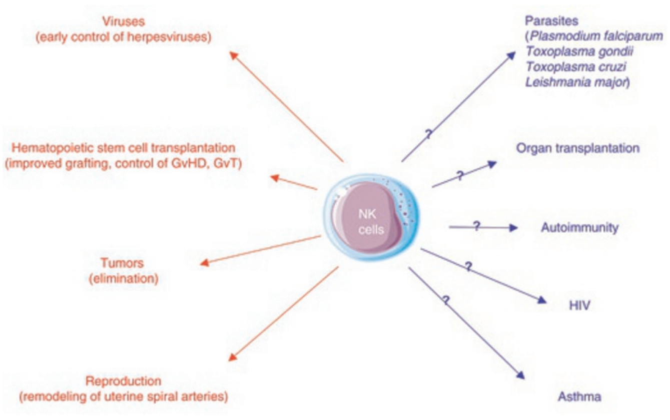

Figure 4 NK cell functions. The known and suspected biological roles of NK cells are indicated in red and blue, respectively.

NK cells as regulatory cells

In addition to their negative feedback exerted on activated macrophages during microbial infections, NK cells act as regulatory cells to influence various other cell types, such as DCs, T cells, B cells and endothelial cells (**Fig. 3**). NK cells can meet DCs in peripheral tissues, as well as in secondary lymphoid organs, and can act on them in two distinct ways[26,73,74]. First, NK cells can kill immature DC in humans and mice, thereby influencing DC homeostasis, but also potentially limiting DC-based vaccination efficacy[75,76]. Conversely, the killing of target cells by NK cells can lead to the cross-presentation of antigens from apoptotic NK cell targets by subsets of DCs. This NK cell–mediated cytotoxicity of target cells induces robust antigen-specific adaptive immune responses involving $CD8^+$ T cells, $CD4^+$ T cells and immunoglobulin G (K. Hoebe, Scripps Research Institute, personal communication). Recognition and killing of target cells by NK cells might thus provide a new and powerful strategy for vaccine development, depending on the experimental and/or clinical design. In mouse allogeneic solid organ transplantation settings, host NK cells suppress alloreactive effector T cell development through their capacity to rapidly eliminate donor-derived DCs present in the graft[77]. Second, by means of IFN-γ and tumor necrosis factor, NK cells can promote the maturation of DCs, which in turn activate NK cells by means of IL-12 (refs. 26,73,74). Recently, CpG oligodeoxynucleotides have been shown to act as anti-inflammatory drugs in a model of mouse arthritis. These TLR9 agonists promote the cross-talk between $CD8\alpha^+$ DCs and NK cells, which leads to NK cell IFN-γ production, which in turn prevents neutrophil recruitment to the joint[78]. The positive feedback loop triggered by NK cells and DCs might thus lead to anti-inflammatory applications.

Besides influencing DC function, NK cells can influence adaptive immune responses by directly acting on T and B cells. In the inflamed lymph node, NK cells can promote the priming of $CD4^+$ T helper type 1 (T_H1) cells by secreting IFN-γ[79,80]. NK cells can also kill activated T cells, unless the T cells express sufficient amounts of classical or nonclassical MHC class I molecules[81]. As a consequence, blockade of CD94-NKG2A inhibitory receptors leads to NK cell cytotoxicity against activated $CD4^+$ T cells, suggesting the use of blocking antibodies to NKG2A to prevent $CD4^+$ T cell–dependent autoimmunity[81]. In the *Fas*-deficient mouse model (previously called *lpr*), NK cells can suppress autoreactive B lymphocytes *in vitro*, and NK cell depletion *in vivo* increases the severity of autoimmunity[82]. NK cell–based negative regulation of inflammation and immune responses might explain the previously reported protective role for NK cells in some autoimmune conditions[83]. Thus, NK cells may not only protect the host against pathological agents, but also against excessive immune response to these agents.

Endothelial cells are primary targets of immunologic attack, and their injury can lead to vasculopathy and organ dysfunction in various pathological conditions, including allograft or xenograft rejection. At least three receptors expressed on NK cells can promote their adherence to endothelial cells: $\alpha_4\beta_1$ integrin (VLA-4) through its binding to VCAM-1, CD62L (L-selectin) through its binding to addressins, and CX3CR1 through its binding to membrane-bound CX3CL1 (fractalkine). CX3CL1 activates NK cells, leading to the killing of endothelial cells, which suggests that NK cells may be involved in the pathogenesis of vascular injury[84], such as the endothelial damage induced during human CMV infection[85]. In organ transplantation, the killing of donor endothelial cells by host NK cells is associated with the failure of their

MHC class I–specific inhibitory receptors to recognize donor MHC class I molecules, severely limiting xenotransplantation protocols[86]. In contrast, NK cells might also promote angiogenesis in other situations, such as pregnancy. Enrichment of uterine natural killer (uNK) cells is indeed observed in the pregnant endometrial tissue in many species[87]. uNK represent a very distinct subset of NK cells that secrete proangiogenic factors such as vascular endothelial growth factor (VEGF), placental growth factor (PLGF) and NKG5 (ref. 88), thereby participating in the remodeling of the feeding arterial systems that support maternal endometrial tissue at sites of implantation and support subsequent placental development. However, the participation of uNK cells in infertility or spontaneous abortion is still a matter of debate[87,89].

Emerging aspects of NK cell biology

In contrast to their protective role in various inflammatory conditions, NK cells can also act as mediators of innate immunopathology. In patients with chronic hepatitis B virus infection, a subset of NK cells contributes to liver inflammation by inducing hepatocyte death through a TRAIL-dependent mechanism[90]. In hepatitis B virus transgenic mice, NK cells also promote liver injury through NKG2D (ref. 91). Moreover, NK cells act detrimentally in experimental sepsis induced by *Streptococcus pneumoniae* or *Escherichia coli* by exacerbating inflammatory responses[92,93]. In a mouse model of diabetes induced by coxsackie virus B4, NK cells contribute to beta-cell islet destruction[94]. Consistent with these data, a significant increase of various NK cell transcripts is detected in destructive forms of the BDC2.5 mouse diabetes model[95]. A potential contribution of NK cells has also been postulated in human inflammatory diseases such as arthritis[96] and sarcoidosis[97].

Little is known regarding the presence and function of NK cells in epithelia. It has been recently reported that NK cells can mediate hapten-specific recall responses, independent of B cells and T cells, in a model of contact hypersensitivity[98]. The involvement of NK cells in memory-type immune responses is quite unexpected and needs to be dissected in depth. Whether the skin infiltration involves hapten-specific NK cell receptors or whether various haptens induce distinct types of inflammation that do or do not promote NK cell infiltration is also unknown. In humans, NK cells have been shown to home to inflamed skin in various conditions, such as vernal keratoconjunctivitis[99], atopic dermatitis[100], psoriasis[101] and lichen planus[24]. NK cells have also been detected in the gut[102], but the physiological significance of these observations remains to be precisely addressed.

The role of NK cells in the control of major life-threatening infections worldwide is complex but deserves attention. This is the case for parasitic infections, including toxoplasmosis, trypanosomiasis, leishmaniasis and malaria[103]. In case of *Plasmodium falciparum* infection, the early production of IFN-γ through cooperation between monocytes/macrophages and NK cells seems to be a very important factor that promotes protective immunity, but field studies are required to firmly establish this point[104]. In the case of HIV infection, NK cell counts and function decrease with AIDS progression[105]. The combination of genetic epidemiology and *in vitro* studies has led to the proposal that an activating KIR, KIR3DS1, by interacting with HLA-Bw4 molecules on HIV-infected cells, activates NK cells, leading to the containment of viral replication[106]. However, direct interaction between KIR3DS1 and HLA-Bw4 remains to be shown[107]. In parallel, it has been reported that a soluble HIV-1 gp41 peptide (3S) induces on uninfected T cells the expression of a ligand for the natural cytotoxicity receptor NKp44 (ref. 108). As a result, NK cells might kill uninfected T cells, thereby promoting their elimination during HIV-1 infection. If confirmed, these results might pave the way for therapeutic strategies against HIV-1 and AIDS.

Concluding remarks

The lack of clear cases documenting NK cell–dependent human disease suggests that NK cells may have redundant functions in several conditions. Nevertheless, *in vitro* observations using human and mouse cells, *in vivo* mouse data, and epidemiologic human data support a role for NK cells in the early control of viral infection, in hematopoietic stem cell transplantation, in tumor immunosurveillance and in reproduction (**Fig. 4**). Other reports indicate that NK cells may also be involved in organ transplantation, in the control of parasitic and HIV infections, in autoimmunity and asthma (**Fig. 4**), but these observations remain to be explored further. Two transgenic mouse models have been reported, one with a constitutive[109] and one with an inducible[14] NK cell–selective depletion. Notably, no spontaneous diseases have been reported in these models in specific pathogen–free housing conditions, but many challenges need to be performed.

Thus, thirty years after the discovery of NK cells, several aspects of NK cell function *in vivo* remain to be unveiled. Yet the emerging view is that NK cells not only participate in the control of various viruses and tumors, but also act as regulatory cells during inflammation and influence subsequent adaptive immune responses.

Note: Supplementary information is available on the Nature Immunology website.

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COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/natureimmunology/.

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