https://www.sciencedirect.com/science/article/pii/S1658387614001083

review

Natural killer cells: In health and disease

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Hematol Oncol Stem Cell Ther 2015; 8(2): 47–55

DOI: http://dx.doi.org/10.1016/j.hemonc.2014.11.006

Abstract Natural killer (NK) cells constitute our bodies' frontline defense system, guarding against tumors and launching attacks against infections. The activities of NK cells are regulated by the interaction of various receptors expressed on their surfaces with cell surface ligands. While the role of NK cells in controlling tumor activity is relatively clear, the fact that they are also linked to various other disease conditions is now being highlighted. Here, we present an overview of the role of NK cells during normal body state as well as under diseased state. We discuss the possible utilization of these powerful cells as immunotherapeutic agents in combating diseases such as asthma, autoimmune diseases, and HIV-AIDS. This review also outlines current challenges in NK cell therapy.

KEYWORDS: Natural killer (NK) cells; NK cells and cancer; NK cells and HIV1; NK cells and autoimmunity; Immunotherapy

Pathogen invasion in our body is counteracted by both adaptive and innate immune cells. The adaptive immune system is represented by B and T cells. B cells play a major role in the humoral immune response, whereas T cells are primarily involved in cell-mediated immune responses. The innate immune system consists of cells and proteins that play a crucial part in the initiation and subsequent activation of the adaptive immune system. They also participate in the removal of pathogens that have been targeted by an adaptive immune response. The main components of the innate immune system are physical epithelial barriers, phagocytic leukocytes, dendritic cells, and natural killer (NK) cells.

NK cells are crucial components of the innate immune system and, as the name suggests, they do not require pre-stimulation to perform their effector functions.[1] Morphologically, they are characterized as large, granular, bone marrow-derived lymphocytes and phenotypically, they are defined as $CD56^{+}$ $CD3^{-}$ in humans. They represent 10% of the cells in the total peripheral blood mononuclear cell (MNC) population of circulating human lymphocytes and they comprise the third largest population of lymphocytes following B and T cells. They are also found in the peritoneal cavity, spleen, liver, lung, lymph nodes, thymus, and in uterus during gestation.

NK-CELL DEVELOPMENT

It is generally accepted that NK cells develop primarily in the bone marrow, similar to B cells and myeloid origin cells. However, recent studies have shown that NK cells can also develop in lymph nodes and liver.[2,3] The generation of NK cells from hematopoietic stem cells (HSC) is a continuous process. In the first step, the HSC shows commitment towards NK-cell lineage. NK-cell precursors (NKP) have been identified in the hematopoietic population, which differentiates into NK cells but not to other lineages. This process is followed by phenotypic and functional NK-cell maturation. In the final step, NK cells undergo homeostasis. Several transcription factors as well as soluble and membrane factors have been identified that regulate NK-cell development and maturation. Transcription factors involved in the generation of NKP include Ets-1, Id2, Ikaros and PU.1.[4,5] Maturation of immature NK cells is regulated by Gata-3 and IRF-2 and functional differentiation of matured NK cells involves CEBP-γ, MEF and MITF. The

cytokine IL-15 has been shown to be essential for NK-cell development, homeostasis and survival.[6] Studies by Freud and Ferlazzo have implicated the role of T cell derived IL-2 in the cytolytic functional maturation of NK cells.[2,7]

NK CELL FUNCTION

Natural killer cells have diverse biological functions which include recognizing and killing virally-infected and neoplastic cells. Circulating NK cells are mostly in their resting phase but activation by cytokines leads to infiltration of these cells into most tissues that contain pathogen-infected or malignant cells.[8,9] NK cells also have an immunoregulatory role as they secrete several cytokines, such as interferon (IFN)-γ, following their ligand interaction with cell-surface receptors. Human NK cells can be classified into two subsets, depending on their immunophenotype and function: $CD56^{dim}$ and $CD56^{bright}$. $CD56^{dim}$ constitutes 90% of the total NK cell population in peripheral blood and these express a low-affinity receptor for the constant region of immunoglobulin G, Fc γ RIIIa (CD16).[10] Functionally, these have high cytotoxic activity. Approximately 10% of NK cells belong to the $CD56^{bright}$ subset and they are mostly involved in the production of cytokines.

The NK cells in the secondary lymphoid tissue such as tonsils, lymph nodes, and spleen are different from the NK cells in the peripheral blood as these are activated by dendritic cells and they secrete cytokines such as interferon, which stimulate a more efficient killing response by the T cells.[7,11]

NK-cell functioning is controlled by a wide range of receptors that are expressed on the cell surface. These receptors are either inhibitory or activating in nature. The family of inhibitory receptors consists of the killer immunoglobulin-like receptors (KIR) or Ig-like receptors (CD158), the C type lectin receptors (CD94-NKG2A) and leukocyte inhibitory receptors (LIR1, LAIR-1). Activating receptors are the natural cytotoxicity receptors (NKp46, NKp44), C type lectin receptors (NKG2D, CD94-NKG2C), and Ig-like receptors (2B4). A particular NK cell typically expresses two to four inhibitory receptors in addition to an array of activation receptors. As different NK cells express different combinations of inhibitory or activating receptors, there is sizeable heterogeneity within the NK-cell population. It is for this reason that NK cells are considered to have the ability to respond to a variety of stimuli and to participate in immune responses under different pathological conditions.

NK-cell cytotoxicity is tightly regulated by a balance between activating and inhibitory signals. The inhibitory NK-cell receptors recognize self-MHC class I molecule, and this prevents NK-cell activation. This explains self tolerance and prevention of host cell killing. It was earlier discovered that NK cells are activated when they encounter cells which lack self-MHC class I molecule. This is known as the 'missing-self' hypothesis.[12] Moreover, NK cells can discriminate between normal host cells and infected or abnormal cells by recognition of MHC class I molecules. Virally infected cells and tumor cells often downregulate MHC class I expression to escape recognition by cytotoxic T lymphocytes (CTL), but this results in their vulnerability towards NK-cell attack. In this condition, activation receptors are no longer suppressed and they induce potent stimulatory signals, therefore tipping the balance in favor of NK-cell activation.[13,14] This condition is often referred to as induced-self recognition.

Once the target is recognized by NK cells, their cytotoxic ability is mainly mediated via two predominant pathways. A membrane-disrupting protein, perforin, and a family of structurally related serine proteases, granzymes, are secreted by exocytosis, which jointly induce apoptosis of the target cell. In the second pathway, a caspase-dependent apoptosis takes place involving the association of death receptors (e.g. Fas/CD95) on target cells with their equivalent ligands such as FasL, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on NK cells, resulting in caspase-dependent apoptosis. Antibody dependent cellular cytotoxicity (ADCC) can also be a mechanism of killing of tumor cells by NK cells as they express a low-affinity Fc receptor for IgG, FcγRIII (CD16).

NK CELLS DURING VARIOUS PHASES OF HUMAN LIFE

Human NK cells are present in fetal liver as early as gestational week 6, and in fetal spleen at gestational week 15.[15] Although fetal liver NK cells are known to have the ability to kill target cells, they are hyporesponsive compared to adult NK cells. This indicates that fetal liver NK cells are functionally immature. It is likely that during the first trimester, NK-cell development is under a dynamic phase. This is followed by a steady phase in the second trimester. The transition from fetal NK-cell development to a more adult-like NK-cell state occurs in the third trimester.[16] Activity of NK cells in newborns is considerably lower compared to adults, as has been shown in

a study by Kaplan *et al.*[17] This inactivation has been accounted for by the lack of activation of pre NK cells *in vivo*. This deficiency may be associated with the susceptibility of newborns to certain viral infections such as herpes viruses, against which NK cells are considered to be the first line of defense.

During pregnancy, peripheral blood NK cells are found to be suppressed both in terms of number and activity.[18,19] NK cells, besides being present in the peripheral blood, can also be detected in the uterus. This set of NK cells is known as uterine natural killer (uNK) cells. uNK cells do not express CD16, unlike peripheral blood NK cells, but they express CD94 and secrete cytokines such as MIP1α, GM-CSF, CSF1 and IFN-γ.[20] It has been suggested that uNK cells are either a distinct subpopulation of peripheral blood NK cells or they could have arisen by tissue-specific differentiation. At the implantation site, uNK cells are the most prominent leukocytes present. During the proliferative phase of the menstrual cycle, uNK cells are few in number. Their level rises significantly during the secretory phase and continues to remain high during early gestation. At 20 weeks' gestation NK cells decrease and are absent in term deciduas.[21,22] They play an important role in controlling trophoblast invasion and express receptors that interact with ligands expressed on trophoblast.[23] NK cells are an important regulator of spiral artery remodeling and maintenance of decidual integrity.[24] Fu *et al.* demonstrated that NK cells regulate pathogenic T helper 17 (Th17) cells at the maternal-fetal interface and thus promote immune tolerance and maintenance of pregnancy.[25] They are also responsible for switching the pro-inflammatory state to the anti-inflammatory state in the endometrium by down-regulating the expression of a soluble decoy receptor (ST2L) receptor on their surface molecule, which binds to IL-33. Imbalance in IL33/ST2 activation can lead to recurrent pregnancy loss.[26]

ROLE IN VARIOUS DISEASE CONDITIONS

The involvement of NK cells has been recognized in various disease conditions. As mentioned previously, one of the primary functions of NK cells is immuno-surveillance of our body. Several *in vitro* studies on mammalian cells, including human cells, and also *in vivo* studies in mice and rats prove that NK cells recognize tumor cells as targets. They control tumor growth and metastasis diffusion *in vivo*. Tumor immuno-surveillance role of NK cells has also been implicated in controlling the growth of B cell lymphomas that spontaneously arise in mice lacking both perforin and β2-microglobulin.[27] An epidemiologic survey of 11-year follow-up shows a link between low NK cell activity in peripheral blood and increased cancer risk in adults.[28] The role of NK cells as host immunity has also been studied in various cases of infections by flaviviruses, such as Japanese encephalitis virus, yellow fever virus, dengue virus, tick-borne encephalitis virus and West Nile virus (WNV). Their role in viral hepatitis, influenza virus and HIV-1 infection is also well documented in several studies.[29–34] Similarly, their role in protecting against respiratory infection by bacteria, viruses such as respiratory syncytial viruses (RSV), and influenza has been elaborately described in murine studies.[35–37] NK cells are assumed to be a major determinant of the development of viral-associated asthma.

In most cases, the role of NK cells is found to be either disease controlling or disease enhancing. For example, in asthma, NK cells contribute towards the progress of T cell mediated allergic airway response during allergen specific sensitization phase.[38,39] Existing evidence also suggests that NK cells are involved in resolving acute allergic airway inflammation.[40] Peripheral blood of asthmatic patients shows enhanced NK-cell activity which decreases upon antigen challenge.[41] This suggests that NK cells migrate from circulation towards lungs and lymphoid organs.[41,42] Similarly, in human autoimmune diseases, changes have been observed in circulating blood NK cells in terms of quantitative as well as qualitative parameters. In many instances of autoimmune disease, a reduction in number of NK cells along with decreased cytotoxic function has been observed.[43,44] *In vivo* studies using experimental autoimmune encephalomyelitis (EAE), which is an animal model of multiple sclerosis (MS), show increased severity and mortality when NK cells are depleted prior to disease induction. EAE animals have cellular infiltration, CNS inflammation, and demylination.[45–47] It is therefore hypothesized that NK cells are involved in the control of autoimmune disease conditions. Clinical trials on MS patients suggest low frequency and activity of NK cells in the peripheral blood but this cannot be ascertained as these studies were conducted using variable methods and low patient sample size.[48–50] On the other hand, the cytotoxicity of NK cells can augment an autoimmune disease. Auto reactive NK cells can lead to the destruction of cells in a target organ. In Type 1 diabetes, NK cells have been found in pancreatic islets only during infection or inflammation, and not under healthy, non-diseased conditions.[51] Preclinical data also

suggest that NK cells are involved in the development of Type 1 diabetes.[52,53] Some studies on Type 1 diabetes patients show that NK cells are either decreased or their function is impaired.[54–56] In rheumatoid arthritis (RA), tissue NK cells have disease promoting functions. In 2005, Laszlo reported that patients with RA have NK-cell accumulation in their synovial fluid.[57] The NK-cell subset, $CD56^{bright}$, found here, secretes more IFNγ compared with blood NK cells from the same patients.[58] However, in systemic lupus erythematosus (SLE), patients show a variable and moderate reduction of NK-cell numbers along with reduced $CD4^{+}CD25^{+}$ Treg cells.[59,60] The function of NK cells is downregulated in these patients and there is a shift from the $CD56^{dim}$ population to the $CD56^{bright}$ subset.[61,62] It is also indicated that NK cells in these patients have a reduced cytotoxic effect.[63] This deficiency of NK cells corresponds with clinical conditions such as nephritis and thrombopenia during SLE. The abnormality in NK-cell number and function could therefore play a role in the inflammatory condition. In other words, NK cells play a protective or disease controlling role to prevent SLE.

It is evident that NK cells act on cells during disease condition either through their receptors or due to the interactions of cytokines. They are known to attack tumor cells when the expression of MHC class I molecules is absent or downregulated. Upregulation of NKG2D ligands on tumor cells can also make them susceptible to NK-cell attack. Most cancer cells engage the NK cell's activating receptors, which triggers its natural kill response. Members of the NK-cell receptor family also contribute towards the defense mechanism against viruses. Infection of mouse or human cells with flaviviruses is known to increase cell-surface expression of MHC class I on infected cells, as evidenced in WNV infection, and therefore they evade NK-cell mediated killing.[64,65] In HIV1 infection, although no specific NK-cell receptors have been identified that recognize HIV1 infected cells, there is a remarkable increase in inhibitory receptors and a decrease in number of activating receptors like NKp30, NKp46 on NK cells.[66,67] *In vivo* condition has shown that NK cell ligand HLA-B Bw4-801 and its receptor KIR 3DS1 form an association resulting in the inhibition of HIV-1 replication and the killing of target cells by NK cells.[32,34] This leads to a decrease in activity of NK cells during HIV1 infection. The abnormality of NK-cell functioning during HIV-1 infection can be credited to viral proteins. HIV-1 gp41, gp120, Nef and Tat have been proven to downregulate NK-cell activity by various mechanisms.[68–71] Evidence of NK-cell receptor involvement is also known in diabetes. Gur *et al.* recently demonstrated that NKp46, the activating NK-cell receptor, binds to an unknown ligand on pancreatic β cells effectively killing them, due to the degranulation of NK cells in mice as well as humans.[51,54] The study concluded that NKp46 is essential for the development of Type 1 diabetes. In humans, this ligand is expressed constitutively in both the young and in adults. But the fact that not all humans become diabetic in spite of possessing the ligand that makes β cells subject to NK-cell attack is because NK cells are not commonly found in the healthy pancreas. In another study, patients with long-standing Type 1 diabetes showed a remarkable low expression of NKp30 and NKp46 activating receptors in their blood in comparison to those of the control group. Also, the expression of NKG2D was found to be reduced relative to the control and irrespective of disease duration. Long-standing patients also displayed reduced perforin mRNA expression.[72] Consistent with these results, a decreased lysis activity by the NK cells was observed by Lorini *et al.* in patients with long-standing diabetes.[73] The reduction in NK-cell activity in these diabetic patients is thought to be a consequence rather than a cause.

An important role is played by cytokines and chemokines which act in conjunction with NK cells to tackle various diseased conditions. IL-12 and IL-18, NK activating cytokines active during late NK-cell differentiation, have been demonstrated to synergistically enhance cytotoxicity against tumor targets and IFN-γ production by NK cells. IFN-γ induces type I immune response and directly acts on cancer cells. IL-12, IL-18 and IFN-γ are also known to have a pro-atherogenic effect.[74] In response to certain viral infections, IFN-α/β is produced, enhancing the NK-cell mediated cytotoxicity and leading to the killing of the viral infected cells. Moreover, many key pathways related to antiviral functions are activated by IFN-γ. IL-21, another cytokine binding the common γ-chain (shared with IL-2, IL-4, IL-7, IL-9, and IL-15), has been demonstrated to favor the onset of the most cytotoxic $CD56^{dim}CD16^{+}$ NK cell subset and to enhance its cytotoxicity. Tumor Necrosis Factor (TNF) is another factor produced by NK cells and which is known to mediate antiviral and immunoregulatory effects. Chemokines produced by NK cells such as MIP-1α are capable of promoting inflammatory processes. In some cases, IL-10, also produced by NK cells, is known to be anti-inflammatory which inhibits Dendritic Cells (DCs). NK cells can lessen

the effect of antigen presentation by Antigen Presenting Cells (APCs) and reduce T cell proliferation.[75] These cells are normally observed to have accumulated at the site of immunization, and they generate cytokines which are involved in the pathogenesis of allergic inflammation. NK cells are indicated to generate IFN-γ, TNF-α, GM-CSF and MIP-1 α upon stimulation with IgE, and also demonstrate cytotoxicity against IgE coated target cells in a Fc γRIII dependent manner.[76]

NK cells interact with various other immune cells in our body both in normal conditions as well as during pathological conditions. In normal and asthmatic lungs, lung resident dendritic cells and macrophages are known to form synapses with NK cells leading to generation of NK derived cytokines and effector molecules involved in local immunity, and at the same time can regulate allergic disease severity.[77] The dynamic nature of cytokine and cellular profile of the microenvironment can influence the development of specific NK subtypes which may lead to conversion from a pro-inflammatory to a pro-resolution NK subtype.[78] If there is any disturbance or defect in this process, then it may lead to more severe inflammation and eventually to airway damage. DCs are known to crosstalk with NK cells through production of cytokines such as IL-12 and IL-18 as well as through cell–cell interactions to promote NK-cell activity against tumors. Crosstalk between NK cells and DCs may be disrupted during HIV1 infection, although this mechanism is not clear. Moreover, it is possible for NK-cell mediated lysis of virally infected cells to be a source of apoptotic bodies for uptake of DCs, which may promote DC maturation and viral antigen presentation to T cells.[79] Another important immune system component, the macrophages, are known to increase the anti-tumor and anti-infection activity of NK cells through their crosstalk.[80–82] Treg cells, part of the adaptive immunity, are also known to interact with NK cells and mostly control their activity during various disease conditions. Treg cells have been seen to suppress NK cells via IL-21 mediation in autoimmune disease conditions.[83] Similarly, in patients with gastrointestinal, colon and prostrate cancers, a high level of Treg cells has been associated with a reduced number of NK cells along with reduced functionality.[84–86] An *in vitro* study has shown that Treg cells from hepatocellular carcinoma patients inhibit NK-cell killing ability. However, during pregnancy, NK cells, along with Treg cells, contribute towards the creation of tolerant conditions for the fetus, and any change in that leads to complications (Table 1).

Table 1. NK cells in disease conditions.

Disease	Role of NK cells	Status of NK cell during disease condition	Possible therapeutic approach	References
Cancer	Immuno-surveillance	Low activity	Adoptive NK cell transfer and enhancement of activatory receptors	27,28,87–96
Viral infection	Immuno-protection	Low number and activity, shift from $CD56^{dim}$ to $CD56^{bright}$	Adoptive NK cell transfer, genetically engineered HIV1 specific NK cells receptors, CCR5 deficient hESC-NK cell transfer	29–37
Asthma	Contribution to IgE mediated immune-response, resolution of airway inflammations	Migration from circulation to lung and lymphoid organs	Adoptive NK cell transfer, *in vitro* or *in vivo* expansion of specific NK cell subsets	38–42
Type 1 diabetes	Disease enhancing	Migration from blood to pancreas? Low expression of NKp30, NKp46 and NKG2D, low perforin in blood NK cells	Targeting NKp46 receptor to reduce auto-destruction of β-cells	51–54,72,73
Rheumatoid arthritis	Disease controlling or enhancing?	Low number and activity in blood, increase in synovial fluid	Blocking inhibitoryNKG2A (to enhance) or RANKL and M-CSF (to control)	44,57,58,97
Systemic lupus erythematosus	Disease controlling	Low number and activity, $CD56^{bright}$ increase, low perforin	Adoptive NK cell transfer	59–63

Abbreviations: hESC – human embryonic stem cells.

THERAPEUTIC APPLICATIONS OF NK CELLS IN VARIOUS DISEASE CONDITIONS

NK cells play a crucial role in attacking tumor cells in our bodies, and are considered a promising tool for cancer therapy. Treatment range over the past two decades has included IL-2 administration to activate the endogenous NK cells or to adoptively transfer IL-2 activated NK cells.[87–91] Autologous NK-cell therapy has been experimented on for the treatment of renal cell carcinoma, malignant glioma, and metastatic breast cancer. However, it was soon recognized that autologous adoptive NK-cell therapy may have certain drawbacks and thus may not be efficacious. The drawback is mostly attributed to the inhibition of NK cells by self-MHC I molecules expressed on the tumor cells. This has led to the use of allogeneic NK cell therapy in trials. In a pioneering study, Ruggeri *et al.* demonstrated that alloreactive NK cells given to patients with acute myelogenous leukemia (AML) could eliminate relapse, graft rejection, and protect them against graft-vs-host disease (GvHD).[92] Later, adoptive cellular transfer of allogeneic NK cells from haploidentical donors was also attempted for treatment of renal cell carcinoma, metastatic melanoma, refractory Hodgkin's disease, and refractory AML.[93] They were also found to be useful against several solid tumors such as neuroblastoma, renal, colon, gastric, and ovarian cancers.[94,95] The trials concluded that NK-cell transfer was safe and efficacious. Similar trials were also conducted recently in patients with recurrent metastatic breast and ovarian cancer.[96] The allogeneic NK cells have the advantage of being derived from healthy donors and have more cytotoxic activity. Moreover, NK cells do not induce GvHD, unlike T cells.

As discussed in the earlier section, the role of NK cells has been established not only in cancer but also in various other disease conditions. Adoptive NK cell therapy can thus be explored for diseases such as asthma, multiple sclerosis, diabetes, arthritis, etc. The effectiveness of NK cells in controlling HIV-1 infection has already been demonstrated in *in vitro* and *in vivo* experiments.[31,33] NK cell therapy can be applied to patients who are refractory to standard highly active antiretroviral therapy (HAART). Besides the option of using NK cells for adoptive transfers, understanding the role of NK cells and their receptors can open up other strategies to treat diseases. For example, during the developmental stages of Type 1 diabetes, the activation of NK cells can be prevented by the administration of specific antibodies for blocking the NKp46 activation receptor. Similarly, in rheumatoid arthritis where the role of NK cells can possibly be protective or disease-enhancing, therapy can be considered accordingly. Inhibitory receptor NKG2A can be blocked, which will stimulate NK cells and thus control the disease. Where NK cells enhance the disease condition, the blocking of RANKL (receptor activator of NF_KB ligand) and M-CSF (macrophage colony-stimulating factor), factors which mediate osteoclastogenesis and bone destruction, can help.[97]

For the purpose of therapeutic applications, allogeneic NK cells can be sourced from umbilical cord blood (UCB), adult donor lymphapheresis products, or even from NK-cell lines such as NK-92. Recently, studies have shown successful *in vitro* derivation of functional NK cells from human embryonic stem cell (hESC) and induced pluripotent stem cell (iPSC).[98–100] hESC and iPSC-derived NK cells have demonstrated potent anti-tumorigenic and anti HIV activity, and are phenotypically similar to those of peripheral blood origin. Moreover, they are considered superior to UCB-derived NK cells because they have higher levels of KIR expression, thus making them more potent. Pluripotent cell-derived NK cells can therefore be an unlimited source for the adoptive transfer of NK cells to treat a range of diseases. However, safety of hESC and iPSC-derived NK cells in terms of potential tumorigenicity needs to be determined before they can be utilized in the clinical set up.

The application of NK cells as immunotherapeutic agent requires several technical developments. NK cells need to be isolated and expanded in sufficient numbers for them to act as effector cells. Moreover, the activity of NK cells needs to be enhanced for better efficacy. Expansion of NK cells has been attempted using cytokines such as IL-2 and IL-15.[101,102] These two cytokines can also help increase the survivability of the NK cells.[103] IL-2 is also thought to potentiate the cytotoxic ability of NK cells. Co-culturing NK cells with accessory cells such as irradiated Epstein Barr Virus (EBV) transformed lymphoblastoid cells, HFWT (a Wilm's tumor derived cell line), and K562 has been reported to enhance NK cell proliferation.[104–106] Activation of NK cells can be achieved by various genetic engineering techniques to augment activating signals and also to downregulate inhibitory signals.[107–111] Similarly, the specificity of NK cells can be increased through genetic modification approaches such as the use of chimeric antigen receptors (CARs)[112–114] (Table 1).

CONCLUSION

Research to date has helped us gain an understanding of NK cell biology in terms of function and role of their receptor interactions. Their task in attacking tumor cells is now well established. However, a clearer picture to determine their specific roles in diseases such as asthma, diabetes, and rheumatoid arthritis is still desired. Further investigation is required to understand the interactions of NK cells with other cells of the immune system such as T cells, dendritic cells, and macrophages. But there is no doubt that NK cells will emerge as major players in the area of cancer treatments, viral infections, including HIV/AIDS, autoimmune diseases, and asthma in the coming decade. The immediate future may see the use of NK cell therapy in combination with chemotherapy, radiotherapy, and surgery for cancer. More focus should be placed on establishing techniques for the isolation and expansion of these cells in their required numbers.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

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