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Natural Killer Cell and its Potential Therapeutic Role in Cancer: A Review

[1]Abebayehu Amenu, [1]Tsehaye Hadush, [1]Alebachew Tilahun, [1]Ayichew Teshale and [2]Abebaw Getachew

[1]Wolaita Sodo University, School of Veterinary Medicine, Ethiopia
[2]Agarfa Agricultural Technical and Vocational Training College, Ethiopia

Abstract: Natural Killer cells are classically considered as innate immune effectors cells involved in the first line of defense against infected and malignant cells. More recently, NK cells have emerged to acquire properties of adaptive immunity in response to certain viral infections such as expansion of specific NK cell subsets and long-lasting virus-specific responses to secondary challenges. Natural killer cells distinguish healthy cells from abnormal cells by measuring the net input of activating and inhibitory signals perceived from target cells through NK cell surface receptors. Acquisition of activating ligands in combination with reduced expression of MHC class I molecules on virus-infected and cancer cells activates NK cell cytotoxicity and release of immune stimulatory cytokines like IFN. In the cancer microenvironment however, NK cells become functionally impaired by inhibitory factors produced by immunosuppressive immune cells and cancer cells. Here summarized recent progress on the role of NK cells in cancer treatment. Describe regulatory factors of the tumor microenvironment on NK cell function which determine cancer cell destruction or escape from immune recognition. Finally, recent strategies that focus on exploiting NK cell anti-cancer responses for immunotherapeutic approaches are reviewed.

Key words: Cytotoxicity · Immunoglobulin-Like Receptors · Major Histocompatibility Complex · Natural Killer Cell · Natural Cytotoxicity Receptor · Tumor

INTRODUCTION

Natural killer cells have originally been described to belong to the innate arm of the immune system [1]. Natural killer (NK) cells are lymphocytes arising from CD34 hematopoietic progenitor cells in the bone marrow. Although NK cells are primarily found in the blood, liver, spleen, bone marrow and, to a lesser extent, in the lymph nodes, inflammation and other factors can trigger NK cell migration into almost any tissue. Natural killer cells were identified on the basis of their ability to lyses tumors cells without prior sensitization. In contrast to B-cells and T-cells, NK cells do not rearrange genes to acquire antigen-specific receptors. Instead, NK cells target tumor cells via an array of germ line-encoded cell surface receptors. Based on this characteristic, NK cells have traditionally been considered to be innate immune cells. However, the observation that some NK cell subsets can be long-lived and show recall responses to certain stimuli has recently challenged this characteristic of adaptive immunity [2].

Natural killer cells are considered to bridge innate and adaptive immunity by the secretion of IFN which enhances MHC class I expression on tumor cells and MHC class II expression on antigen-presenting cells like monocytes/macrophages and dendrite cells [3]. Aside from their role in initial responses against infection and cancer, it has become evident, that NK cells also contribute to the induction of adaptive anti-cancer T cell as well as B cell responses [4, 5].

The role of the immune system in elimination of tumor growth will be seen here particularly, recent data concerning the role of NK cells in the elimination of spontaneous tumors, or the role of adaptive immunity in the maintenance of tumors as a chronic disease. Four classes of cells have been established to have key roles in the immune response against tumors and consequently the immune system is totally involved in this action. These cells are: Natural killer cells that provide innate immune response; CD8+ T lymphocytes that represent the adaptive immune response; (NKT) natural killer T-cells, which connect the two classical type of immune response

Corresponding Author: Alebachew Tilahun, Wolaita Sodo University, School of Veterinary Medicine, Ethiopia.

and so are usually regarded as "transitional" immune responses; TREGS that recognize an antitumor immune response as an autoimmunity response and manage to inhibit [6]. Hence, to some extent NK cells are able to prevent excessive immune activation and autoimmune pathology. Their classification as solely innate immune cells are currently further challenged since there is now evidence that under certain conditions NK cells can acquire similarities to adaptive immunity such as expansion of specific subsets and antigen-specific responses [7].

The objectives of this seminar paper are:

- To show the potential therapeutic role of natural killer cell in cancer.
- To review the function, receptors, ligands and regulation of the natural killer cell.
- To know how tumor cells, escape immune system of the body.

Natural Killer Cell: Natural killer cell is a cell that can react against and destroy another cell without prior sensitization to it. Natural killer cells are part of our first line of defense against cancer cells and virus-infected cells. Natural killer cells are small lymphocytes that originate in the bone marrow and develop without the influence of the thymus. A natural killer cell attaches to a target cell and releases chemical that breach its cell wall and causes it to lyses [8].

Historical Note of Natural Killer Cell: In 1975, Natural killer cells were first identified in mice as a distinct sub-population of lymphocytes endowed with the capacity to kill tumor cells without prior sensitization. Since then, NK cells underwent a fascinating metamorphosis in scientists' minds from dumb, unspecific killer machines to highly sophisticated and well educated detectives of harmful changes in cellular self and pivotal catalysis of adaptive T-cell responses. Major advances in the current understanding of NK cell biology originated from the models of 'missing-self' and 'induced-self' recognition. These models propose that NK cells, in contrast to their sister lymphocytes, T and B cells, do not recognize foreign antigens, but rather are 'self-centered' by detecting changes in self-molecules displayed at the surface of antilogous cells. This MHC class I-dependent recognition mode explains why virally infected or malignant cells with an impaired MHC class I expression are attacked by NK cells, whereas 'healthy' autologous cells are protected from NK cytotoxicity [9, 10].

Natural killer cell mediated cytolysis of MHC class I-deficient cells provides an important safeguard for the MHC class I-restricted elimination of 'dangerous' cells by CD8 T cells. Natural killer cells can detect a state of 'missing-self' by MHC class I-specific inhibitory receptors. The ensuing characterization of several activating NK receptors, foremost of the NKG2D receptor that detects cell stress-induced self-ligands on 'dangerous' cells, led to the proposition of the 'induced-self' recognition model [11, 12]. The latter complements the 'missing-self' recognition model by stating that NK cell triggering requires the expression of inducible ligands of activating NK receptors. Altogether, it is now common sense that the activation of NK cells depends on an intricate balance between activating and inhibitory signals [13]. Healthy cells express NK-inhibiting MHC class I molecules and no or few activating NK ligands leaving NK cells quiescent. In contrast, 'dangerous' cells stimulate NK cell responses by an increased expression of activating NK ligands and a reduced MHC class I outfit. However, a full appreciation of these concepts and, in particular, of NK-mediated tumor surveillance needs to await the thorough molecular characterization of the ligands of activating NK receptors [14].

Comparison of Natural Killer Cells and Other Leucocytes: Natural killer cells have characteristics in common with other leucocytes and may be considered a transitional lymphocyte bridging the innate and adaptive immune system. They do share common killing mechanisms with cytotoxic T cells, such as the use of perforin and granzymes. Similarly, to T-cells, they also produce IFN-γ- [13]. Unlike T-cells, they are not able to produce IL-2, important for NK cell activation and proliferation. Natural killer cells differ from T-cells in that they are ready for an immediate action and they do not depend on APCs to be able to recognize their targets as T-cells do. They do not require selection or expansion of specific clones in order to exert their functions. It has recently been found that some NK cells develop into memory NK cells, a feature that was thought to be exclusive for T and B-cells [15].

Natural Killer Cell Receptors and Their Ligands: Natural killer cells distinguish between normal and abnormal cells by using a complex array of cell surface receptors that control their activation, proliferation and effectors functions. NK cell receptors are expressed on relatively large subpopulations of cells making them well suited for early immune responses since clonal expansion is not needed. The main groups of receptors are: Killer cell

immunoglobulin-like receptors (KIRs), natural cytotoxicity receptors (NCRs), CD94 receptors, NKG2D receptor, CD16 receptors and DNAM-1 receptors [13].

Killer Cell Immunoglobulin-Like Receptors: Most killer cell immunoglobulin-like receptors are inhibitory and recognize MHC class I molecules. Ligand binds by these receptors result in suppressed cytotoxicity and cytokine secretion by both NK and T cells [13]. Killer cell immunoglobulin-like receptors belong to the Ig super family of receptors. They are type I transmembrane glycoproteins and are named according to the number of extra-cellular immunoglobulin domains and the length of their intracellular tails. This tail determines whether they are activating (short) or inhibitory (long). Killer cell immunoglobulin-like receptors recognizes certain HLA-A, HLA-B and HLA-C molecules. The function of the activating KIRs is more uncertain, although it has been shown that the activating KIR2DS1 receptor recognizes HLA-C alleles and contributes to NK alloreactivity [16]. It has been shown that the presence of donor KIR2DS1 partially protects against leukemia relapse after hematopoietic stem-cell transplantations [17].

Natural Cytotoxicity Receptors: Natural cytotoxicity receptors belong to the immunoglobulin super family of receptors. This group of receptors trigger NK mediated killing and cytokine secretion. The Natural cytotoxicity receptors family includes NKp46 and NKp30 that are expressed on both resting and activated NK cells and NKp44 that is expressed only on activated NK cells. The NCRs have been shown to interact with wide spectra of cellular, bacterial, parasitic and viral ligands. Many aspects of the ligand binding are still unclear. These receptors also recognize ligands on tumor cells [18].

CD94 Receptors: These receptors recognize the non-classical HLA-E molecule. HLA-E presents leader fragments from other HLA class I molecules. CD94 heterodimers are formed by the CD94 glycoprotein bound to either NKG2A or NKG2C. CD94 binding to HLA-E inhibits NK-cell cytotoxicity and cytokine production. The CD94 receptor activates NK-cells and it is thought to contribute to self-tolerance of the NK cells [19].

Natural Killer Group 2-Member D Receptor: The activating receptor NKG2D interacts with self-molecules that are up-regulated on stressed cells. The NKG2D receptor is constitutively expressed on most NK-cells and recognizes the stress-induced MHC class I-like molecules MICA/B, as well as ULBPs, commonly expressed on tumor cells and virally infected cells [20].

CD16: The activating CD16 receptor on NK cells recognizes antibody-coated target cells and mediates antibody-dependent cellular toxicity (ADCC). This low affinity Fc receptor is present on essentially all CD56dim peripheral blood NK cells. These receptors bind to the Fc portion of IgG1 and IgG3 antibodies. Upon recognition of antibody-coated cells, NK cells are rapidly activated and degranulation resulting in target cell killing [20].

DNAX Accessory Molecule-1: DNAX accessory molecule-1 belongs to the Ig-super family of receptors. It is constitutively expressed on all NK cells and has two different ligands, CD155 and CD112 (Nectin-2). Both ligands are present on many cancer cells making them sensitive to NK cell mediated killing. A DNAX accessory molecule-1 associate with LFA-1 on the cell surface and mediates activating signals DNAM-1 controls NK cell cytotoxicity and IFN-γ production in response to a wide range of cancer cells and infected cells. Its ligands, CD112 and CD155, have been found in different pathological conditions and recent evidence suggests that their expression is up-regulated by cellular stress [21].

Natural Killer Cell Functions: Natural killer cells have several tasks, such as the elimination of infected and transformed cells. They also produce high amounts of cytokines. In order to avoid auto-immunity it is important that NK cells are self-tolerant. One theory explaining the ability to kill foreign and transformed cells, while leaving "self" cells unharmed is the "missing self" hypothesis [20].

The "Missing Self"- Hypothesis: Major histocompatibility complex class I molecules are present on most nucleated cells in the body. They present peptides to cytotoxic T cells and may also be recognized by NK cell receptors. Natural killer cells express inhibitory receptors recognizing MHC class I molecules. These interactions inhibit NK cell cytotoxicity and cytokine production. Cells expressing these ligands are spared from NK cell lyses. In the absence of these ligands, NK cells may become activated. Such activation is dependent on activating NK cell receptors recognizing target cell

ligands. According to the 'missing self' hypothesis, one function of NK cells is to recognize and eliminate cells that fail to express the full set of self MHC-class I molecules. The "missing self"- hypothesis proposed that NK cells kill cells that have lost their ability to express self MHC class I molecules or express allogeneic MHC molecules, not able to engage the inhibitory NK cell receptors. The loss of MHC class I molecules is a common event in cancers and virally-infected cells. Natural killer cells can in this way eliminate cells that are insensitive to cytotoxic T cells [20].

Integration of Inhibitory and Activating Signals: Natural killer cells must integrate activating and inhibitory signals in order to respond properly. When activating NK receptors are engaged, NK cells may become activated and kill surrounding cells if not controlled by the inhibitory class I receptors. The inhibitory receptors usually have a dominant effect over the activating receptors. Infected cells may up-regulate ligands for activating receptors while MHC class I expression is reduced. This activates NK cells and the infected cells are eliminated [22].

Stress- Induced Self-Recognition: Natural killer cells express activating receptors that recognize stress-induced ligands. These ligands are expressed at very low levels (or not at all) under normal conditions but are up-regulated by various forms of cellular stress such as viral infections and cancer development [23]. The activating receptors primarily involved in this recognition are NKG2D and DNAM-1 [22].

Killing Mechanisms of Natural Killer Cell: Natural killer cells kill target cells mainly by inducing apoptosis. This is similar to cytotoxic T cells. The release of cytotoxic granules containing pore-forming perforin and granzymes play a dominant role in this process [19]. NK cells may also induce apoptosis by TNF α-related apoptosis inducing ligand (TRAIL). TRAIL induces apoptosis of target cells by interacting with death receptors present on activated cells and tumor cells. Natural killer cells may in this manner eliminate tumor cells and limit the presence of activated cells, such as neutrophils and T- cells at the site of infection. TNF-α released by NK cells may also induce apoptosis of target cells by triggering caspase 8. In addition, NK cells express Fas ligand. Fas ligand may engage Fas receptor on target cells (present on most cells) and induce apoptosis [24].

Cytokine Production: Natural killer cells respond to signals from other innate immune cells, including dendrite cells, macrophages and pathogen-infected tissue cells. These signals are relayed in the form of cytokines such as IL-1, IL-10, IL-12, IL-15 and IL-18. NK cells respond by secreting cytokines such as tumor necrosis factor-α (TNF-α) and interferon γ (IFN-γ). In this way, following the triggering of innate immune cells by pattern recognition receptors, NK cells can relay and amplify cytokine signals. When TNF-α is released it may induce apoptosis of the target cells, while IFN-γ activates macrophages for phagocytosis and pathogen lyses. IFN-γ also induces MHC class I expression on tumor cells sensitizing them to CD8+ T cell killing. The combination of TNF-α and IFN-γ may also induce senescence in tumor cells [25]. It has been shown that NK cells secrete several other factors, including immune regulatory cytokines such as IL-5, IL-10, IL-13 as well as the growth factor GM-CSF and the chemokines MIP-1α, MIP-1β and IL-8 [26].

Regulation of Natural Killer Cell Activity: Activity during development of natural killer cells that fail to express inhibitory receptors to at least one 'self' MHC class I type are rendered anergy to prevent reactivity against healthy 'self' cells; a concept referred to as 'education' or 'licensing' [27, 28]. Natural killer cells that express inhibitory receptors in combination with activating receptors are able to react against abnormal 'non-self' cells. Transfer of NK cells from an MHC class I-sufficient mouse to an MHC class I-deficient mouse (and vice versa) can reset NK cell responsiveness [29, 30].

Hence, the fate of reactivity or hypo responsiveness of mature NK cells appears to be continuously modulated by trafficking through environments with changing levels of inhibitory molecules. Consistent with this hypothesis, persistent failure of engaging inhibitory receptors in an MHC class I-deficient tumor microenvironment reduces NK cell responsiveness unless NK cell are re-stimulated with NK cell-activating cytokines like interleukin-2 (IL-2) [31]. Thus, lyses of cancer cells is triggered by low expression of ligands for NK cell inhibitory receptors, such as killer cell immunoglobulin-like receptors (KIR) and CD96, in combination with increased expression of ligands for NK cell activating receptors, such as NKG2D and natural cytotoxicity receptors [32].

Role of Natural Killer Cells in Cancer Therapy: A role for natural killer cells in the rejection of transplanted hematopoietic tumors or chemically-induced tumors was

demonstrated in various mouse models, in which NK cells prevented tumor outgrowth and supported the formation of primary and secondary tumor-specific CD8 and CD4 T cell responses [11, 33]. High numbers of tumor-infiltrating NK cells and cytotoxic T cells are often associated with a better prognosis for cancer patients [34]. It is conceived that NK cells preferentially mount responses against hematological malignancies or cancer metastasis which are more easily accessible through the circulation [35].

Autologous Natural Killer Cell Therapy: In autologous NK cell therapy, the patient's own NK cells are extracted and manipulated *in vitro* to enhance their response to tumor cells. The manipulated cells are then re-infused into the patient. This procedure has had little clinical benefit probably due to inhibitory KIRs recognizing self MHC class I on the tumor cells. An important finding from these trials was that in order for donor cells to expand in the recipient, it was necessary to create space for the graft. This requires elimination of recipient leucocytes that would otherwise compete for growth factors and cytokines [20].

Allogeneic NK Cell Therapy: Allogeneic NK cell therapy refers both to donor lymphocyte infusions, i.e. transfer of mature allogeneic NK cells and transplantation with hematopoietic stem cells that eventually develop into mature allogeneic NK cells. These allogeneic NK cells are capable of mediating graft versus host defense effects. Heliocentrically transplantation is one form of allogeneic hematopoietic stem cell transplantation. This treatment protocol was originally developed to overcome the lack of HLA-matched donors. In heliocentrically transplantation the related donor and recipient share only one HLA haplotypes. The patients receive high doses of hematopoietic stem cells depleted of T cells in order to avoid graft versus host defense. They are also subject to strong cytotoxic and immunosuppressive conditioning regime to prevent graft rejection. This procedure has shown the potential of NK cells in cancer treatment. The beneficial effects of this procedure may be explained by the missing-self hypothesis. Subsets of donor-derived NK cells that are not restrained by MHC class I molecules in the patient may have graft versus leukemia potential. There is no risk of graft versus host defense reactions since recipient cells, apart from the leukemia cells, lack activating ligands for donor NK cells [23].

The importance of KIRs in HSCT has recently been shown. Patients receiving grafts from donors with the KIR2DS1 genotype had a reduced risk of relapse from acute myelogenous leukemia after both unrelated and matched sibling donor allogeneic transplant [22].

Monoclonal Antibodies: Many monoclonal antibodies, such as rituximab, bind tumor cells. The low affinity Fc receptor CD16 present on NK cells efficiently induces antibody-dependent cellular cytotoxicity (ADCC) of cells coated with IgG1 and IgG3 antibodies [22]. Another monoclonal antibody that makes use of ADCC by NK cells is Alemtuzumab. It is an IgG1-type monoclonal antibodies directed against CD52 on tumor cells. Alemtuzumab is used in the treatment of refractory CLL. This antibody kills target cells by complement-activation and/or ADCC, but seems also capable of inducing direct apoptosis via caspase-dependent and -independent mechanisms [36].

The monoclonal human antibody IPH-2101 of the IgG4 isotype has been tested in patients with myelomatosis. This antibody blocks interaction of KIR2D receptors with HLA-C. This should theoretically enhance NK cell cytotoxicity [37]. But no clinical response was observed. Several monoclonal antibodies are now in clinical trials. Their number has been growing constantly in the last ten years and they offer an interesting and promising field of development in the treatment of many different types of cancer [36].

Use of Cytokines: There is successful use of lymphokine activated killer cells to treat patients with advanced cancer. Lymphokine activated cells were generated by culturing peripheral blood mononuclear cells with high doses of IL-2. This resulted in a mixture of activated NK and T cells. In these early studies, lymphokine activated cells were generated *in vitro* from the patient's own PBMCs and they were re-infused later together with high doses of IL-2. High doses of IL-2 however lead to vascular leakage and hypotension. In addition, IL-12, IL-15 and IL-18 have been used alone or in combination with histamine dihydrochloride, to enhance NK and T-lymphocyte proliferation and cytotoxicity. This protocol enhanced NK cytotoxicity and tumor control with significant improvement in leukemia-free survival [38].

Chimeric Antigen Receptor (CAR) NK Cells: Chimeric antigen receptor (CAR) cells express genetically modified receptors. T or NK cells are transfected with these receptors in order to endow them with a distinct specificity. The chimeric receptor may contain parts of a

monoclonal antibody reacting to a specific tumor antigen. There are ongoing discussions about the advantages of using NK cells as compared to T cells as chimeric antigen receptor vectors. One of the features that might make NK cells preferable is their relatively short lifespan. It may give a better control over possible side-effects. Allogeneic NK cells are expected to induce an immune response and be rejected after a few days and even autologous NK cells should disappear relatively rapidly [37].

Natural killer cells have additional advantages over T cells because they are not exclusively depended on the CARs. As mentioned earlier, NK cells display spontaneous killing of tumor cells by several different mechanisms such as NKp30, NKp44, NKp46, NKG2D and DNAM-1. They also express CD16 rendering them capable of killing antibody-coated tumor cells. Fast and strong production of IFN-γ and GM-CSF could also enable CAR-NK cells to induce anti-tumor responses by surrounding cells [36].

Limitation of Natural Killer Cell Therapy in Cancer: Tumor cells are known to use various strategies to escape immune control. Natural killer cells are perhaps the best studied mediators of the innate immune defense against cancers. Their activity may be affected in several ways by the developing tumors. Natural killer cells may be rendered unresponsive; their numbers may be reduced or they may fail to recognize tumor cells. Most of these effects can be attributed to either changes in the tumor microenvironment or the tumor cells themselves [39].

Changes in the Microenvironment: The secretion of immunosuppressive cytokines such as IL-10 by tumor or stromal cells results in the down-regulation of NKp30, NKp44 and NKG2D. Down-regulation of these activating receptors reduces NK cytotoxicity and cytokine production. Another immunosuppressive cytokine, TGF-β, has been shown to inhibit NK function during chronic interaction with tumor cells. TGF-β antagonizes IL-15 which is important for NK cell proliferation and activation. Shedding of soluble ligands is another mechanism by which tumors inhibit NK cell function. Shedding of ligands may down-regulate or block activating NK cell receptors. Chronic ligand-induced stimulation may also render NK cells unresponsive. Many tumor cells release soluble NKG2D ligands (MICA/B and ULBPs). These soluble ligands have been identified in the sera of patients with various cancer types including glioma, neuroblastoma, breast, lung, colon and ovarian carcinomas as well as in acute myelogenous leukemia patients [25].

Changes in Cancer Cells: Some tumor cells escape T-cell mediated control by decreasing their expression of MHC class I molecules. This down-regulation however may increase their susceptibility to NK mediated killing, although tumor cells often exhibit other transformations that protect them from NK cell lyses. Other cancer cells, such as acute myelogenous leukemia, may display increased levels of MHC class I molecules, inhibiting NK cell function. This may lead to NK cell energy due to the chronic interaction with inhibitory NK cell receptors. CML patients often express high levels of MICA inducing weak NKG2D expression. This may also result in escape from NK cell killing. There may also be a selection for cancer cells that have lost their NK-activating ligands. NK susceptible tumor cells are killed while resistant tumor cells expand. In this manner, NK cells can contribute to immune-editing of cancer cells [25].

CONCLUSION

In recent years, a variety of review has been developed to use natural killer cells in treatment of cancer. An improved understanding of NK cell cytotoxicity should lead to progress in clinical applications of this approach. In addition, natural killer cells are lymphocytes arising from CD34+ hematopoietic progenitor cells in the bone marrow. Although NK cells are primarily found in the blood, liver, spleen, bone marrow and, to a lesser extent, lymph nodes, inflammation and other factors can trigger NK cell migration into almost any tissue. NK cells were identified on the basis of their ability to lyses tumors cells without prior sensitization. They also contain receptors that may activate or inhibit NK cell activity. Receptors characterized include major histocompatibility complex (MHC) class I ligand killer-cell immunoglobulin-like receptors (KIRs). KIRs can serve as activating receptors or inhibitory receptors. Inhibitory KIRs have a transmembrane domain with long cytoplasmic tail. Activating KIRs have shorter cytoplasmic tails and activate NK cells by association with adaptor molecules. They bridge innate and adaptive immunity by the secretion of IFN which enhances MHC class I expression on tumor cells and MHC class II expression on antigen-presenting cells like macrophages and dendrite cells. Tumor cells are known to use various strategies to escape

immune control. NK cells are perhaps the best studied mediators of the innate immune defense against cancers. Their activity may be affected in several ways by the developing tumors.

Based on this conclusion the following recommendation were forwarded:

- The clinical applications of autologous natural killer cells therapy to the patients with cancer to enhance their response to the tumor cells should be practiced.
- Clinician should use allogeneic natural killer cell therapy which refers transfer of allogeneic natural killer cell and transplantation with hematopoietic stem cells.
- Finally, the clinician must recognize various methods cancer cells escape immune control of the body.

REFERENCES

1. Cerwenka, A. and L.L. Lanier, 2001. Natural killer cells, viruses and cancer. Nat. Rev. Immunol., 1: 41-49.
2. Gregoire, C., R.B. Herberman, M.E. Nunn and H.T. Holden, 2007. The trafficking of natural killer cells. Immunol. Rev., 220: 169-182.
3. Vivier, E., E. Tomasello, M. Baratin, T. Walzer and S. Ugolini, 2008. Functions of naturalkiller cells. Nat. Immunol., 9: 503-510.
4. Smyth, M.J., J. Swann, E. Cretney, N. Zerafa, W.M. Yokoyama and Y. Hayakawa, 2005. NKG2D function protects the host from tumor initiation. J. Exp. Med., 202: 583-588.
5. Krebs, P., M.J. Barnes, K. Lampe, K. Whitley, K.S. Bahjat, B. Beutler, E. Janssen and K. Hoebe, 2009.NK-cell-mediated killing of target cells triggers robust antigen-specific T-cell-mediated and humoral responses. Blood, 113: 6593-6602.
6. Bhardwaj, N., 2007. Harnessing the Immune System to treat cancer. Clin Invest, 117: 1130-1136.
7. Sun, J.C., S. Ugolini and E. Vivier, 2014. Immunological memory within the innate immune system. Embr, 33: 1295-1303.
8. http://www.medicinenet.com about definition of natural killer cell.
9. Algarra, I., T. Cabrera and F. Garrido, 2000. The HLA crossroad in tumor immunology. Hum. Immunol., 61: 65-73.
10. French, A.R. and W.M. Yokoyama, 2003. Natural killer cells and viral infections. Curr Opin Immunol, 15: 45-51.
11. Diefenbach, A., A.M. Jamieso, S.D. Liu, N. Shastri and D.H. Raulet, 2000. Ligands for the murine NKG2D receptor: expression by tumor cells and activation of Natural killer cells and macrophages. Nat. Immunol., 1: 119-126.
12. Raulet, D.H., 2004. Interplay of natural killer cells and their receptors with the adaptive immune response. Nat Immunol., 5: 996-1002.
13. Lanier, L.L., 2005. Natural killer cell recognition. Annual Review of Immunology, 23: 225-274.
14. Galeotti, L., L. Zamai, C. Ponti, P. Mirandola, G. Gobbi and S. Papa, 2007. NK cells and cancer. J. Immunol., 178: 4011-4016.
15. Sun, J.C., 2009. Adaptive Immune Features of Natural Killer Cells. Nature, 457: 557-561.
16. Pende, R., 2009. Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR ligand and re definition of inhibitory KIR specificity. Blood, 113: 3119-3129.
17. Venstrom, M.D., 2012. HLA-C–Dependent Prevention of Leukemia Relapse by Donor Activating KIR2DS1. New England Journal of Medicine, 367: 805-816.
18. Kruse, P.H., 2014. Natural cytotoxicity receptors and their ligands. Immunology and Cell Biology, 92: 221-229.
19. Bogen, B., L.A. Munthe, M. Carretero, C. Cantoni and T. Bellon, 1997. The CD94 and NKG2-A C-type lectins covalently assemble to form a natural killer cell inhibitory receptor for HLA class I molecules. Eur. J. Immunol., 27: 563-567.
20. Geller, M. and J.S. Miller, 2011. Use of allogeneic NK cells for cancer immunotherapy. Immunotherapy, 12: 1445-1459.
21. Ferrari, A., M.J. Smyth and J. Martinez, 2014. DNAM-1 control of natural killer cells functions through nectin and nectin-like proteins. Immunology and Cell Biology, 54: 237-244.
22. Davies, T.M., 2014. Opportunities and limitations of natural killer cells in adoptive therapy. Nat. Immunol., 115: 6543-94.
23. Vivier, E., S. Ugolini, D. Blaise, C. Chabannon and L. Brossay, 2012. Targeting natural killer cells and natural killer T cells in cancer. Nat. Rev. Immunol., 12: 239-252.
24. Schuster, I.S., 2014. TRAIL+ NK Cells Control CD4+ T-Cell Responses during Chronic Viral Infection to Limit Autoimmunity. Immunity, 8: 646-656.

25. Markus, L.K., 2014. How cancer cells escape immune system. Advances in Immunology, 122: 2345-2349.
26. Fauriat, L. and N. Ljunggren, 2010. Regulation of NK-cell cytokine and chemokine production by target cell recognition. Blood, 115: 2167-76.
27. Anfossi, N., P. Andre, S. Guia, C.S. Falk, S. Roetynck, C.A. Stewart, V. Breso, D. Reviron, D. Middleton, F. Romagne, S. Ugolini and E. Vivier, 2006. Human Natural killer cell education by inhibitory receptors for MHC class I. Immunity, 25: 331-342.
28. Kim, S., J. Poursine-Laurent, S.M. Truscott, L. Lybarger, Y.J. Song, L. Yang, A.R. French, J.B. Sunwoo, S. Lemieux, T.H. Hansen and W.M. Yokoyama, 2005. Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature, 436: 709-713.
29. Elliott, J.M., J.A. Wahle and W.M. Yokoyama, 2010. MHC class I-deficient natural killer cells acquire a licensed phenotype after transfer into an MHC class I-sufficient environment. J. Exp. Med., 207: 2073-2079.
30. Joncker, N.T., N. Shifrin, F. Delebecque and D.H. Raulet, 2010. Mature natural killer cellsreset their responsiveness when exposed to an altered MHC environment. J. Exp. Med., 207: 2065-2072.
31. Ardolino, M., C.S. Azimi, A. Iannello, T.N. Trevino, L. Horan, L. Zhang, W. Deng, A.M. Ring, S. Fischer, K.C. Garcia and D.H. Raulet, 2014. Cytokine therapy reverses Natural killer cell anergy in MHC-deficient tumors. J. Clin. Invest, 124: 4781-4794.
32. Thielens, A., E. Vivier and F. Romagne, 2012. NK cell MHC class I specific receptors (KIR): from biology to clinical intervention. Curr. Opin. Immunol., 24: 239-245.
33. Kelly, JM., P.K. Darcy and J.L. Markby, 2002. Induction of tumor-specific T cell memory by NK cell-mediated tumor rejection. Nat. Immunol., 3(1): 83-90.
34. Stojanovic, A. and A. Cerwenka, 2011. Natural killer cells and solid tumors. J. Innate Immun., 3: 355-364.
35. Schreiber, R.D., L.J. Old and M.J. Smyth, 2011. Cancer immunoediting: integratingimmunity's roles in cancer suppression and promotion. Science, 331: 1565-1570.
36. Keating, K., 2002. The rapeutic role of alemtuzumab in patients who have failed fludarabine: results of a large international study. Blood, 42: 345-354.
37. Korde, N., 2014. A phase II of pan-KIR2D blockade with IPH2101. Haematologica, 99: 81-83.
38. Rosenberg, S.A., 1985. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. New England Journal of Medicine, 313: 1485-1492.
39. Moretta, S., 2014. Human NK cells: From surface receptors to the therapy of leukemias and solid tumors. Frontiers of Immunology. NK Cell Biology, 5: 4321-4327.