The role of natural killer cells in chronic myeloid leukemia

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Chronic myeloid leukemia is a neoplasia resulting from a translocation between chromosomes 9 and 22 producing the BCR-ABL hybrid known as the Philadelphia chromosome (Ph). In chronic myeloid leukemia a proliferation of malignant myeloid cells occurs in the bone marrow due to excessive tyrosine kinase activity. In order to maintain homeostasis, natural killer cells, by means of receptors, identify the major histocompatibility complex on the surface of tumor cells and subsequently induce apoptosis. The NKG2D receptor in the natural killer cells recognizes the transmembrane proteins related to major histocompatibility complex class I chain-related genes A and B (MICA and MICB), and it is by the interaction between NKG2D and MICA that natural killer cells exert cytotoxic activity against chronic myeloid leukemia tumor cells. However, in the case of chronic exposure of the NKG2D receptor, the MICA ligand releases soluble proteins called sMICA from the tumor cell surface, which negatively modulate NKG2D and enable the tumor cells to avoid lysis mediated by the natural killer cells. Blocking the formation of sMICA may be an important antitumor strategy. Treatment using tyrosine kinase inhibitors induces modulation of NKG2DL expression, which could favor the activity of the natural killer cells. However this mechanism has not been fully described in chronic myeloid leukemia. In the present study, we analyze the role of natural killer cells to reduce proliferation and in the cellular death of tumor cells in chronic myeloid leukemia.

Keywords: *Leukemia, myelogenous, chronic, BCR-ABL Positive; Killer cells, natural; killer cell lectin-like receptor subfamily D; Protein kinase inhibitors/pharmacology*

Introduction

Natural killer (NK) cells, part of the innate immune system, possess antitumor cytotoxicity. These cells differ from the T and B lymphocytes in that they are larger, do not require prior sensitization, and on their surfaces have CD16 and CD56 markers, which are responsible for the cytotoxic action.[1,2]

Cellular death mediated by NK cells occurs as a result of recognition by the different classes of receptors of NK cells, of the major histocompatibility complex (MHC) on the surface of tumor cells and by the action of the lytic granules in the NK cells.[2,3]

Once activated, NK cells undergo morphological changes in which the lytic granules move in the direction of the site of interaction with the target cell. Shortly afterwards, the external membrane of the granule merges with the cytoplasmic membrane and the contents of the granule, the most important components of which are perforin and granzyme molecules, are expelled into the synaptic space. The perforins produce pores in the target cell membrane, altering its permeability and causing osmotic lysis. The granzymes induce apoptosis assisted by the perforins.[2]

Susceptibility of target cells to the action of the NK cells is inversely proportional to their expression of MHC suggesting that the NK cells recognize and attack cells with low MHC-I expression. This recognition mechanism is a crucial aspect of the innate immune system, because the T cells only recognize antigens by means of the MHC. Loss of MHC expression therefore results in the cells being 'out of reach' of T cells.[4]

CD56 and CD16 markers exist on the surface of NK cells and there are two different cell subtypes, which differ according to the expression of CD56. Most NK cells, known as $CD56^{dim}$ cells, have a low expression of CD56 and a high expression of CD16. Predominant (~90%) in the peripheral blood circulation, the main function of these cells is to provide natural cytotoxicity. The other subgroup of NK cells is characterized by a high expression of CD56 and a low or zero expression of CD16. These are termed $CD56^{bright}$ and are equivalent to ~10% of the total population of NK cells. The main function of these cells is to produce cytokines.[2] The $CD56^{dim}$ cells contain a higher concentration of lytic granules. Both of the NK cell subtypes show similar cytotoxicity following treatment with interleukin-2 (IL-2).[5]

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NK cells can act on oncoproteins in chronic myeloid leukemia (CML) patients.[6,7] This neoplasia is the result of a genetic abnormality characterized by the presence of the Philadelphia chromosome (Ph), which results from a translocation between chromosomes 9 and 22 [designated as t(9;22)(q34;q11)].[8-10] This translocation forms the breakpoint cluster region (BCR) gene in chromosome 22, and the Abelson leukemia virus (ABL) gene in chromosome 9, thus inducing the appearance of the BCR-ABL gene fusion in chromosome 22 q- or chromosome Ph and the reciprocal ABL-BCR gene fusion in chromosome 9q+.[10,11]

The active BCR-ABL gene promotes phosphorylation of a chimeric protein. This protein is responsible for the proliferation of a clone of malignant myeloid cells in the bone marrow due to the excessive tyrosine kinase activity that it induces, which confers a high resistance to cellular death on the leukemic cell. It is this activation that is responsible for CML pathogenesis.[12]

The mechanisms of resistance that cause greater cell growth and proliferation in the presence of the Ph chromosome compared to normal cells are not fully understood.[13] Studies have indicated that control of tyrosine kinase activity is essential in the treatment of CML.[14,15] Drugs used to inhibit this process lead to apoptosis of malignant cells, hence reducing tumor proliferation.[14,16]

Research conducted *in vitro* has demonstrated that some of the drugs that inhibit tyrosine kinase exert an inhibitory effect on the immune system by discouraging cell proliferation and suppressing the action of NK cells.[17,18] However more recent work conducted *in vivo* does not support this notion, since increases in NK and T cells were observed in patients undergoing treatment with these drugs.[19]

The mode of action of NK cells in CML has still not been fully described. The present work therefore uses a review of the literature to analyze the participation of NK cells in reducing proliferation and in cell death in CML.

NK cell activating and inhibitory receptors

The ability of NK cells to distinguish infected and malignantly transformed cells from normal cells depends on their expression of inhibitory and activating receptors.[1] There are four main families of receptors found in NK cells. The C-type lectin, killer immunoglobulin-like receptor (KIR) and leukocyte immunoglobulin-like receptor (LIR) families possess both activating and inhibitory receptors. However, the natural cytotoxicity receptor (NCR) family only possesses activating receptors.[2,6,20]

Inhibitory receptors recognize MHC-I, which is often expressed in healthy cells but rarely found in cancerous cells, while the activating receptors of NK cells recognize structures that are present in both normal and tumor cells.[21] The influence of the inhibitory routes is greater when MHC-I is recognized compared to the activating routes. Meanwhile when the activating receptor ligands are stimulated, the number of these ligands increases, enabling the activating routes to increase and dominate the action of the inhibitory receptors, which provides NK cells with the capacity to destroy cells that express MHC-I molecules. It is believed that the inhibitory signal prevails if the inhibitory and activating signals are equal.[20,21]

Common to the different families of NK cell inhibitory receptors is the immunoreceptor tyrosine-based inhibitory motifs (ITIM) in their cytoplasmic tails. The first family of receptors includes those similar to the C-type lectin activator of NK group 2 (NKG2), which are heterodimers that possess the CD94 subunit. The AB (CD94/NKG2A/B) members of this family recognize the human leukocyte antigen E (HLA-E), and provide an inhibitory signal. Other members, such as CD94/NKG2C, also recognize HLA-E, however they provide an activating signal. They possess cytoplasmic ITIMs, which act as NK cell activating receptors. The CD94/NKG2E/H produces an activating signal, but its ligand is unknown.[2]

Another component of this family is the receptor member D (NKG2D), which possesses an activating signal and, despite not interacting with CD94, recognizes the transmembrane proteins related to MICA and MICB molecules (major histocompatibility complex class I chain-related genes A and B) and the UL-16 protein-ligand family (proteins ULBP1, ULBP2 and ULBP3).[2,20,22]

The second family of receptors includes the KIRs. Fourteen genes of the KIR family, located in chromosome 19q13.4, have been described.[20] The number and composition of genes varies between individuals and their expression varies among NK cells. KIRs are responsible for helping to identify infectious agents and transformed cells, which are recognized according to the presence or absence of HLA surface molecules. The immunological response on the part of the NK cells therefore depends on the concentration of HLA on the surface of the target cell. The members of this family have two or three extracellular domains that are similar to immunoglobulin. KIRs recognize different alleles of the HLA-A, B and C molecules. The sequence of peptides linked to the MHC is important for recognition by KIRs. The HLA interaction with KIRs is characterized by rapid binding and detachment, which is coherent with the fact that NK cells are able to recognize MHC molecules in various cells within a short time interval. The inhibitory signal emitted by NK cells as a result of the recognition of MHC molecules by KIRs is short-lived, allowing the same NK cell to continue and destroy a negative target cell. Some members of the KIR family possess a cytoplasmic tail that lacks ITIMs, which enables them to act as activating receptors.[23,24]

Finally, there is the family of immunoglobulin-like inhibitory receptors, the immunoglobulin-like transcripts (ILTs) or leukocyte immunoglobulin-like receptors (LIRs) or CD85. One of the members of this family, ILT-2, has a wide

specificity for many MHC class I alleles. However, its ligands have still not been fully identified.[20]

In the inhibitory receptors the ITIMs are essential for signaling the MHC molecules. They recruit phosphatase enzymes that are antagonistic to the effect of the kinases present in the signaling made by the activating receptors. As a result, there is a reduction in signaling by activating receptors.[25] Only some activating receptor ligands are known, such as CD16, which is a low affinity receptor for the Fc portion of immunoglobulin G (IgG) and whose function involves antibody dependent cytotoxicity.[24]

The linking of the activating receptors of NK cells with the HLA class I ligands (HLA-A, B and C) stimulates the production of cytokines that direct the migration of large numbers of cells to target locations, resulting in the death of cells exhibiting the ligand. A characteristic common to the activating receptors is the presence of the kinase enzyme in the cytoplasmic tail. CD16 and other activating receptors contain immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic tail.[24]

Another NK cell receptor family consists exclusively of activating receptors known as natural cytotoxity receptors (NCR), including NKp46, NKp44 and NKp30. These markers are more reliable in the identification of NK cells, since the expression of NCRs is restricted to these cells. The members, NKp46 and NKp30, are expressed in NK cells in the peripheral blood circulation, while NKp44 is only found in activated NK cells. This family has an important participation in cytolytic activity against tumor cells mediated by NK cells however the ligands of these receptors remain to be identified.[2]

Some members of the KIR and CD94/NKG2 families of MHC-specific receptors do not possess ITIMs, as already mentioned. However, they associate with molecules exhibiting ITAM, and release activating signals to NK cells. These members include KIR2DS, CD94/NKG2C and CD94/NKG2E/H. In humans, the NKG2D expressed in NK cells recognizes MICA, MICB and ULBP-1, 2, and 3 molecules. These ligands are not usually found in large quantities in normal cells, are regulated by stress or DNA damage, and are frequently found in tumor cells. The NKG2D expression level can increase in NK cells when there is exposure to IL-15. These receptors can be used by the NK cells in immune vigilance against tumor cells.[26]

Anti-leukemic action of NK cells in chronic myeloid leukemia

NK cells have cytotoxic activity against malignant cells in different types of leukemia, providing a front line defense against tumor cells.[2] In patients with leukemia, the number of NK cells appears to gradually decrease as the disease progresses from the chronic phase to blast crisis; additionally NK cells isolated from patients at an advanced stage of the disease show reduced cytotoxicity.[6] As NK cells are able to exert cellular cytotoxicity and initiate an adaptive immune response after the release of the cytokine interferon-γ (IFN-γ), they consequently fulfill an important role in the antitumor immune response.[27]

The activation of the NKG2D immunoreceptor is expressed in cytotoxic lymphocytes, and stimulates the reactivity of NK cells after recognition of these ligands (NKG2DL) that are widely expressed in malignant cells but that are not normally expressed in healthy tissue.[5] Recent studies using rats have demonstrated that deficiency of NKG2D resulted in reduced *in vitro* cytotoxic activity in certain tumors, while there was an increased susceptibility to primary tumorigenesis *in vivo*.[28,29] Furthermore, the transfection of weakly immunogenic tumor cells with marked NKG2DL increased the sensitivity of the cells to lysis mediated by NK cells *in vitro* and *in vivo* in mouse models,[30] confirming the important role of NKG2D in tumor immune vigilance. The interaction between NKG2D and MICA or MICB could potentially increase many innate antitumor responses of NK cells and antigen-specific T cells.[31]

Tumor cells extracted from patients with different types of leukemia, including CML, expressed heterogeneous levels of NKG2DL.[29] Different types of ligands to the NKG2D receptor can be found in tumor cells, including MICA, MICB, ULBP1 and ULBP2.[30,32] Nonetheless, in all leukemia subtypes the ligand showing greatest activity was MICA.[29]

In CML, translocation of the BCR/ABL gene affects dendritic cells, enabling them to activate NK cells by increasing the expression of NKG2D ligands.[33] The BCR-ABL gene directly controls the expression of NKG2DL and the antitumor reactivity of the NK cells is directly dependent on the quantity of NKG2DL on the cellular surface with MICA being the most expressed.[29,30,34] Hence in CML, it is by means of the NKG2D/MICA interaction that NK cells exercise their cytotoxic role against tumor cells.

In chronic exposure of NKG2D, its MICA ligand can secrete soluble proteins produced on the surface of tumor cells, denominated sMICA.[35,30] Increased serum levels of sMICA reflect tumor expansion, since healthy tissues present significantly lower levels of sMICA.[30] The release of sMICA with chronic exposure of NKG2DL expressed in tumor cells, induces a negative modulation of the NKG2D that remains on the surface of NK cells of patients with CML and other types of cancer, facilitating the escape of tumor cells from lysis mediated by NK cells.[36] Blocking of sMICA production may be an important clinical strategy for an antitumor response.[37]

Treatment of CML is by tyrosine kinase inhibitors, with imatinib (also known as STI571 or Glivec®) being the first line therapy. This drug was approved for use in CML patients at the start of the chronic phase, prolonged acceleration phase and the final acute phase (blast crisis).[14] After specific inhibition of tyrosine kinase by imatinib, the levels of sMICA diminish, and the expression of NKG2D in T cells is normalized.[30] This reduction of sMICA could therefore stimulate cellular lysis mediated by NK cells. Meanwhile,

immunotherapy with imatinib interferes in the expression of MICA and MICB molecules, altering the formation of an efficient immunological synapse between leukemic cells and NK cells. As a result, the immunogenicity of the BCR-ABL leukemia cells may be affected, hindering the development of a specific immune response and reducing susceptibility to cytolysis mediated by NK cells.[30,38] More recent studies have indicated that imatinib does not seem to be prejudicial to cytotoxicity or to the production of cytokines by NK cells.[39]

Patients with CML who present resistance or intolerance to therapy using imatinib have been treated with second generation therapeutic drugs such as dasatinib (also known as BMS354825 or Sprycel®) or nilotinib (AMN107 or Tasigna®).[14,17] These drugs have produced responses in patients treated during the chronic and accelerated phases of CML.[14] Dasatinib substantially reduces the reactivity of NK cells by inhibiting signaling pathways but without influencing their viability. Nilotinib has a lesser impact on the cytotoxicity exercised by the NK cells and inhibits the production of cytokines by these cells by inducing cellular death of $CD56^{bright}$ NK cells.[39,40]

It has been demonstrated *in vitro* and *in vivo* that NK cells possess important anti-leukemic activity, and that these cells may be involved in the control of malignant clones in CML. Different therapeutic drugs have been used in the treatment of CML, ultimately causing reduced expression of the MICA and MICB ligands, hence altering the functioning of NK cells. Despite advances in the understanding of NK cells, their potential for use in treating patients with CML is still not well established. Further studies will be needed before immunotherapy using NK cells is accepted in the clinical practice.

Conclusions

The activation of the NKG2D immunoreceptor is expressed in cytotoxic lymphocytes, thus the reactivity of NK cells is stimulated following recognition of NKG2DL. The BCR-ABL gene directly controls the expression of NKG2DL and the antitumor reactivity of NK cells depends directly on the quantity of these receptors on the cell surface. In CML, production of sMICA inhibits the anti-leukemic action of NK cells and favors tumor survival. During treatment with tyrosine kinase inhibitors the expression of NKG2DL is modulated which may favor the action of NK cells.

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