Natural Killer Cells in Cancer: An Overview

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Abstract
Natural Killer cells (NK cells) are cells of the innate immune system that are important players in mounting an immune response against viral infections and tumors. NK cells have a variety of mechanisms in order to detect and attack their target cells. In this review, the roles of NK cells in anti-tumor immunity have been discussed. NK cells use a combination of cell surface receptors and secreted factors in order to attack tumor cells and prevent tumor growth. In addition, NK cells act as an important mediator in the activation of the adaptive immune system, thereby resulting in a sustained anti-tumor immune response. Thus a high NK cell number in the tumor is indicative of a positive prognosis. Therefore, NK cell proportion is an important readout in order to evaluate the efficacy of novel anti-tumor therapies. However, a novel subset of NK cells that can suppress the immune response has recently been described. These 'regulatory' NK cells differ from conventional NK cells in the expression of certain cell surface markers, and secrete immune suppressive cytokines. Thus, immune monitoring studies that use cell surface marker analysis to determine NK cell numbers as a readout for efficacy of experimental therapies need to re-assess their NK cell detection strategy and differentially identify the different NK cell subsets. This would help better predict the prognostic effect of certain therapies, as well as pave the way for novel therapies targeting tumor-mediated immune suppression.
Keywords: NK cells, innate immune system, tumors, immune suppression

Introduction

Natural Killer cells (NK cells) are cytotoxic lymphocytes that play a critical role in the innate immune system. NK cells are usually characterized by the presence, absence or fluorescent intensity of certain cell surface markers, as determined by flow cytometry. In humans, NK cells are identified as $CD3^-$ $CD56^+$. Further, based on the fluorescent intensity of CD56, NK cells can be further sub-classified into $CD56^{bright}$ and $CD56^{dim}$ cells. In mice, they are observed to be $CD3^-NK1.1^+$ or $CD3^-NKp46^+$ (1-3). NK cells represent 5–15% of circulating lymphocytes in humans and can be further categorized into subpopulations based on maturation status (4). As the first line of defense, NK cells have the unique ability to recognize stressed cells (typically virus-infected cells or tumor cells) and are able to mount a rapid immune response in order to eliminate their target cells (5). Importantly, NK cells act as a bridge between the innate and the adaptive immune system, activating T cells, dendritic cells (DCs) and macrophages in order to elicit a more robust and long-term immune response (1). For these reasons, NK cells have gained special significance in tumor immunology and cancer immunotherapy.

NK cells in cancer immunosurveillance

Natural killer cells attack and kill cells that they consider to be dangerous (cancer, foreign or virus-infected cells) and therefore are major players in cancer immunosurveillance (6). NK cells have developed several mechanisms for distinguishing healthy cells from cancerous cells, which form the basis of NK cell activation. These mechanisms consist of a complex mix of signals from a variety of receptors, both stimulatory and inhibitory. The intensity of signaling through either type of receptor dictates the NK cell response. i.e. increased signaling through

the inhibitory receptors leads to tolerance or inhibition of immune response, while increased signaling through the stimulatory receptor leads to activation of an immune response.

NK cells express inhibitory receptors for major histocompatibility complex (MHC) class I complex, viz. the Ly49 receptors in mice, killer immunoglobulin-like receptors (KIRs) in humans, and the CD94-NKG2A heterodimer in both species. Binding of self-MHC class I is a major mechanism for the tolerance of NK cells to self-tissue, and allows their 'education' in order to distinguish between self and non-self tissues (7). Cells undergoing malignant transformation often down-regulate MHC Class I in order to evade the immune system, which may alert the NK cells about their potential as target cells. However, loss of MHC Class I expression alone is not sufficient to elicit an NK immune response. In addition, the malignant cells also need to over express certain NK activation markers in order to affect NK cell recognition.

As mentioned earlier, in tumor cells upon cellular transformation, surface MHC-I expression is often reduced or lost to evade recognition by antitumor T cells. In parallel, cellular stress and DNA damage lead to upregulated expression of ligands for NK cell-activating receptors such as NKG2D, NKp46, NKp30, NKp44 and CD226 (8-13), (14-16). Binding of NK cell activating receptors to their ligands leads to NK cell activation and subsequent tumor cell death. Several studies in mice have supported the notion that NK cells are responsible for the eradication of tumor cells. In these studies, syngeneic tumor cells were implanted in mice that either were genetically deficient in NK cell function or depleted of NK cells using neutralizing antibodies (17-20). Eliminating NK cells in these models often led to a more aggressive tumor growth and metastasis (21). Thus, NK cells play a crucial role in inducing an early immune response to tumor cells.

Mechanisms of tumor cytotoxicity by NK cells

NK cells can exhibit natural cytotoxicity against certain tumor cells in the absence of pre-immunization or stimulation (22-24). $CD56^{dim}$ NK cells, which make up the majority of circulating cells, are the most potent cytotoxic NK cells against tumor cells. As described earlier, NK-cell recognition of tumor cells by inhibitory and activating receptors is complex, and two recognition models—'missing-self' and 'stress-induced self'—might be used to detect tumor cells. NK cells thus activated are thus able to directly or indirectly exert their antitumor activity to control tumor growth and prevent metastasis using direct as well as indirect mechanisms.

Direct NK-mediated anti-tumor immunity

NK cells directly kill target tumor cells through several mechanisms: (a) *Release of apoptosis-inducing granules:* Cytoplasmic granules containing perforin and granzymes lead to tumor-cell apoptosis in a caspase-dependent and -independent manner (25, 26). Perforin induces perforations in the tumor cell membrane, thus allowing entry to Granzymes into the tumor cells and leading to apoptosis; (b) *Death receptor-mediated apoptosis:* NK cells express ligands such as Fas ligand (FasL) or TNF-related apoptosis-inducing ligand (TRAIL), which can induce tumor-cell apoptosis by interacting with their respective receptors, Fas and TRAIL receptor (TRAILR), on tumor cells (27-30). TNF-α produced by activated NK cells can also induce tumor-cell apoptosis (31); (c) *Secretion of various effector molecules:* Effector molecules, such as cytokines, mediate antitumor functions in various ways, including hindering tumor angiogenesis and stimulating adaptive immunity (32, 33). Exposure of tumors to NK cells is also associated with nitric oxide (NO) production, which leads to tumor DNA fragmentation and cell lysis (34, 35); (d) *Antibody-dependent cytotoxicity:* NK cells can sometimes express CD16, a marker that

can interact with antibody receptors on tumor cells in order to induce antibody-dependent cellular cytotoxicity (ADCC) in tumor cells (36-41).

Indirect NK-mediated antitumor immunity

Apart from directly killing tumor cells, NK cells also activate components of the adaptive immune system such as DCs, macrophages, and T cells by producing various cytokines (IFN-γ, TNF-α and IL-10), as well as chemokines and growth factors (42). Activated NK cells produce IFN-γ, which in turn activate naïve $CD8^+$ T cells to become cytotoxic T lymphocytes (CTLs). IFN-γ also helps to differentiate $CD4^+$ T cells toward a T helper1 Th1 phenotype (an inflammatory phenotype) in order to promote CTL differentiation (43-45). In addition, cancer cells killed by NK cells could be phagocytosed by DCs, inducing them to mature and present antigen to T cells in order to generate antigen-specific CTL responses (45-48).

A 11-year follow-up study in patients indicated that low NK cell cytotoxicity was associated with increased cancer risk (49). In patients with colorectal carcinoma, gastric carcinoma and squamous cell lung cancer, high levels of tumor-infiltrating NK cells are associated with a favorable outcome suggesting that NK cell infiltration into the tumor tissues represents a positive prognostic marker (50-52). Using flow cytometry for CD56 detection, Geissler et al. showed that a high percentage of CD56+ NK cells was associated with increased survival in renal cell carcinoma. Therefore it is not surprising that in pre-clinical as well as clinical studies of novel immunotherapies, the levels of NK cells in the tumor as well as peripheral blood is routinely detected by flow cytometry, and presence of high levels CD56+ cells is seen as a positive indication towards tumor remission and increased disease-free survival (53-57).

'Regulatory' NKs

Recent studies have started to describe a subset of NK cells that play a role in immune suppression by regulating the activation of other immune cell subsets (58-61). 'Regulatory' NK cells, or better known as $CD56^{bright}$ NK cells, are phenotypically different from immune activating NKs, and display high surface expression of CD56, are $CD16^{-/dim}$, express the inhibitory receptor NKG2A, and do not express killer cell immunoglobulin-like receptors (KIRs). $CD56^{bright}$ NK cells were first considered "immunoregulatory" by Cooper et al., due to increased production of immunosuppressive cytokines and reduced cytotoxicity compared to $CD56^{dim}$ NK cells (62).

In several studies, it has now been established that $CD56^{bright}$ NK cells regulate other immune cells belonging to both the innate and adaptive immune system. Deniz et al. directly purified IL-10-secreting and non-secreting NK cell subsets from peripheral blood and were among the first to report the ability of IL-10 secreting NK cells to suppress T cell function (63). Thus, there exists a dynamic relationship between NK cells with T cells. Traditionally believed to only promote T cell activation, it is now understood that NK cells can also inhibit T cell–mediated immune responses in a variety of contexts, including autoimmunity, viral infection and anti-tumor immunity (64-69). NK cell–mediated regulation of T cells has been observed in mouse studies where *in vivo* depletion of NK cells improved antiviral T cell responses and resulted in the clearance of lymphocytic choriomeningitis virus (LCMV) (64, 70). In humans, NK cells from patients with chronic hepatitis B virus (HBV) infection were able to kill HBV-specific $CD8^+$ T cells in a TRAIL-receptor-dependent manner (71, 72). In addition to hampering T cell function, some studies have reported that suppressive NK cells produce IL-10, inhibit B cell function, and

weaken immune responses by modulating DC function and by killing $CD8^+$ T cells (47, 73-78). Crome et al. recently described a novel immune cell population (described as $CD56^+CD3^-$ cells) that were characterized as being $CD56^{bright}CD16^-CD94^+NKG2D^+KIR^+NKp30^+NKp46^+$ lymphocytes, which could limit T cell cytokine production and expansion. While the authors refrained from classifying these cells as a subset of NK cells, this novel cell population expressed several cell surface markers that are present in NK cells, specifically KIR and NKp46, with NKp46 regulating interactions with, and suppressing T cells (79) (Figure 1). Thus, several studies have reliable identified an immunosuppressive NK cell subset. However, further studies need to be performed in order to determine the differential expression on cell surface markers and secreted cytokines between conventional and regulatory NKs.

Potential of NK cells as a biomarker for disease prognosis

In cancer patients, immune monitoring studies are routinely carried out in order to evaluate or predict response to therapy. For immune monitoring, immune cell composition in the blood or in the tumor (Tumor infiltration lymphocytes (TILs)) are detected by a variety of mechanisms including flow cytometry and immunohistochemistry. TILs specimens that possess a high percentage of NK cells (as detected by the presence of cell surface markers) are usually associated with better prognosis and increased survival (33, 51, 52). However, recent studies have substantiated the presence of an immunosuppressive NK phenotype. While the specific cell surface markers have yet to be fully elucidated for this subset, most studies have characterized these cells as being $CD56^{bright}$ and secreting IL-10. These findings have tremendous implications for immune monitoring studies that look at TILs to evaluate and predict the prognosis of the patient. The expression of many NK cell markers on regulatory NK cells (albeit at different levels) underscores the need for careful evaluation of these immune cell subsets in TILs before basing prognosis and survival predictions off of NK cell numbers. Furthermore, functional analysis of NK cells from TILs needs to be performed in order to assess their net contribution in the tumor microenvironment.

Conclusions

NK cells form the first line of defense against tumor immune detection and elimination. Furthermore, they play an important role in activating the adaptive immune system, leading to a more powerful and long-lasting immune response against tumors. These abilities have collectively rendered NK cells as a predictive biomarker for better prognosis and improved response to cancer therapy. However, with the recent identification of an immunosuppressive NK cell subtype, which possesses a partial overlap in cell surface characteristics with conventional NK cells, there is now a greater need for routine functional characterization of NK cells in TILs in order to conclusively assess response to therapy and disease prognosis.

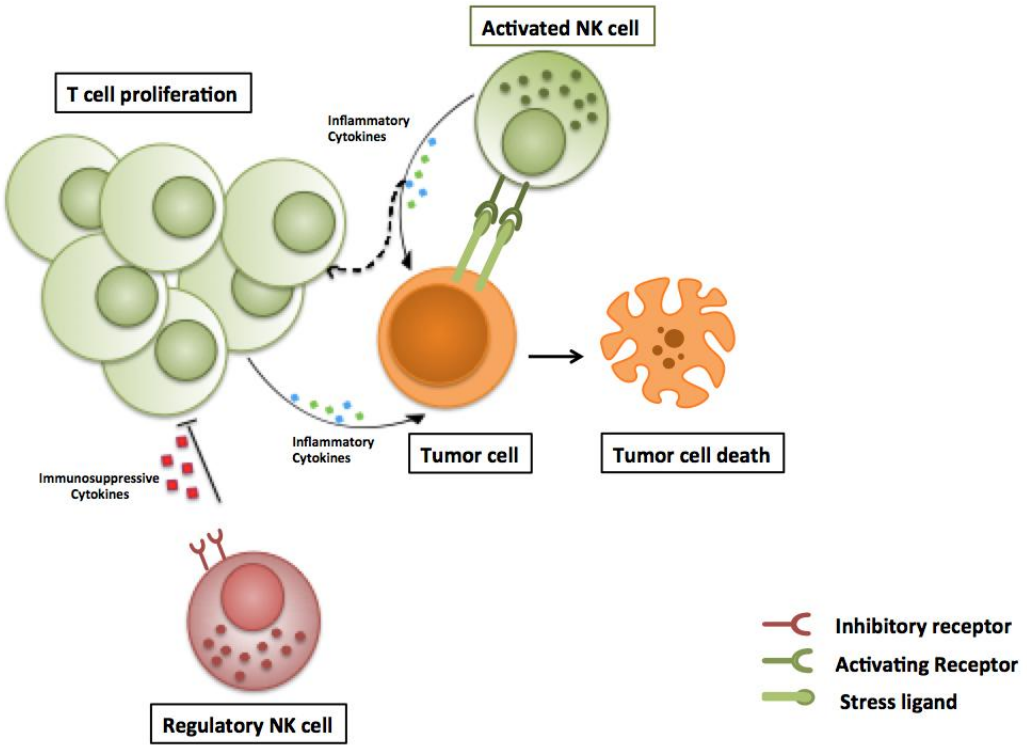

Figure 1: Role of NK cells in mediating and inhibiting tumor cell death

Expression of NK activating ligands on tumor cells can lead to NK cell activation and tumor cell death. In addition, inflammatory cytokines released during NK cell activation can activate cytotoxic T cells, which in turn may also contribute to tumor cell death. Regulatory NK cells, if present, can release immunosuppressive cytokines, which can hamper anti-tumor T cell response.

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