Natural killer (NK) cells are innate lymphoid cells which account for 5–15% of cells in peripheral blood. NK cells develop in the bone marrow and then undergo maturation to acquire different effector functions. During maturation, NK cells express chemokines and adhesion receptors which facilitate their migration from the bone marrow via the blood to different lymphoid and non-lymphoid tissues where they ultimately localize. NK cells are detected in lymphoid tissues including spleen, bone marrow, lymph nodes, and thymus and non-lymphoid tissues, including blood, lungs, liver, colon and uterus. The distribution of NK cells is not static and changes in response to myriad chemokines whose secretion is triggered by infection and malignancy. NK cells defend against pathogens and tumorigenesis by killing the infected or malignant cells in a sequence of steps. NK cells recognize target cells with absent or low major histocompatibility complex-I (MHC-I) expression.4–8 Activation of circulating or localized resting NK cells in tissues is triggered by an imbalance in the activation signals (natural killer cell p46 related protein (NKP46), natural killer group 2D (NKG2D), cluster of differentiation (CD) 16, and lymphocyte-function-associated antigen-1,4–6) and inhibitory signals (NK2A, killer cell lectin-like receptor G1, and T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), etc.) that originate from abnormal cells and the microenvironment. In addition to activating and inhibitory receptors, NK cells also express adhesion molecules (2B4, CD27, CD28, CD226) that are important in mediating adhesion and extravasation of NK cells into the tissue microenvironment.10–11 NK cells mediate killing of target cells via ADCC and antibody-dependent cell-mediated cytoxicity (ADCC); and release of cytokines such as IFN-γ and TNF-α and the granzymes.12–14 NK cells also induce apoptosis of the target cell via tumor necrosis factor (TNF)-related apoptosis-inducing ligand and Fas ligand, and by directly releasing lytic granules such as perforin and granzyme-B.15–17

Abstract

Natural killer (NK) cells are a gatekeeper of the body’s innate defense system against cancers and infections. A growing body of literature from us and others finds that NK cells promote anti-cancer immune surveillance, and that defects in NK cell development are associated with poor clinical prognosis of cancers. In preclinical studies, NK cells were found to drive tumor regression and delay tumor relapse. Because NK cells are potentially less damaging to the body and are easier to develop than T cell-based therapies, efforts are being made to improve NK cell cytokotoxicity and in vivo persistence for use as an adoptive, off-the-shelf immunotherapy. In this review, we discuss how tumor-intrinsic and -extrinsic factors suppress NK cells in the cancer microenvironment. We also outline current strategies that restore NK surveillance in cancer and challenges facing the clinical use of NK cell-based therapies.

Keywords
Natural killer cells; Cancer; Tumor microenvironment; NK cell-based therapies.
cell-mediated cytotoxicity (ADCC) where the Fc receptor CD16 (FcγRIIIa) on NK cells binds to antibody coated target cells and lyases them.  

Additionally, NK cells release cytokines and chemokines that activate surrounding immune cells.  

Dendritic cells (DC), plasmacytoid dendritic cells (PDC), mast cells, basophils, eosinophils, and neutrophils are shown to network with NK cells at the site of the inflammation. Crosstalk between NK cells and DCs generates interleukin (IL)-15, IL-12, IL-23, IL-27, and IL-18, which in turn further activates NK cells and interferon gamma (IFN-γ) production. IFN-γ produced by NK cells promotes DC activation and induces T helper 1 (Th1) polarization and CD8+ T cell-mediated immune responses.  

Studies in humans and in experimental mouse models demonstrated the importance of NK cells in protecting against virus-induced tumorigenesis. In virus-infected mouse models of prostate adenocarcinoma and lymphomas, cancer aggressiveness was shown to be positively associated with NKGD2 deficiency. Tumors are caused by the ubiquitous murine polyomavirus in immunocompromised hosts. In immunocompetent hosts, NK cells and γδ T cells have been shown to delay murine polyomavirus-induced tumor formation. Even in humans, NK cells resist the development of virus-induced tumors such as those driven by human papilloma virus, Epstein-Barr virus (EBV), Human T-cell leukemia virus, Kaposi sarcoma virus, Hepatitis B virus, Hepatitis C virus and Merkel cell polyomavirus.  

Despite being innate immune cells, more recently, NK cells were shown to have immunological memory, a feature of adaptive immune cells. NK memory responses were observed in mice after infection, allergic reactions, and vaccination.  

Because NK cells are cytotoxic lymphocytes with immunological memory, they are attractive candidates for cell-based immunotherapy. Moreover, unlike B and T cells, NK cells do not cause graft-versus-host disease (GVHD) making them a potentially safe, off-the-shelf, living cell therapy.  

In murine tumor models, NK cells resist tumorigenesis and clear primary as well as metastatic tumor cells. The first evidence that established the importance of NK cells in anticancer immune surveillance came from a methylcholanthrene-induced fibrosarcoma mouse model in which depletion of NK cells resulted in faster tumor growth. Due to their antitumorigenic effect, NK cells are the first line of defense against tumors and NK cell infiltration has been associated with improved overall survival. In a pancreatic ductal adenocarcinoma murine model, the Fms-like tyrosine kinase 3 ligand reduced frequencies of pathogenic Th17 cells and increased the numbers and effector functions of cytotoxic CD8+ T cells. Consequently, defective NK cell-mediated immune surveillance in cancers has far-reaching impacts on global anti-cancer host immunity.  

In cancer patients, we and others have found NK surveillance to be suppressed by numerous mechanisms: NK cell numbers are reduced in the tumor microenvironment, NK cytotoxicity is reduced, tumor cells are rendered resistant to NK cell-mediated lysis, NK cells from other sites fail to infiltrate tumor tissue, NK cell-mediated ADCC is defective, other NK-interacting immune subsets such as DCs and T cells are suppressed in function, and NK cells get exhausted due to hyperactivation.  

In mouse models and patients with cancer, we and others have observed that reduction in NK cell numbers is caused by defective NK cell homeostasis, including perturbed cycling and maturation. Specifically, in patients with B- and T-cell acute lymphoblastic leukemia (ALL), we observed significantly increased frequencies of immature and poorly cytotoxic NK cells and a concomitant reduction in the frequencies of functional cytotoxic NK cells. Similarly, in mouse models of solid tumors, including hepatocellular and breast cancer, others have observed a reduction in peripheral and tumor-infiltrating mature NK cells required for ADCC, and an increase in the expression of inhibitory receptors including CD85j on tumor cells that block ADCC. Defective NK cell maturation impairs NK cell-mediated lysis of tumor cells because immature NK cells exhibit reduced expression of activation receptors such as DNAX accessory molecule-1 (DNAM-1), NKGD2D, CD16, and Nkp30, and increased expression of inhibitory receptors such as NKG2A.  

In addition to defects in NK cells themselves, the resistance of tumor cells to NK cell-mediated cytosis also arrogates anti-cancer NK surveillance. For example, cancer cells shed the NKG2D ligands and major histocompatibility complex class I chain-related proteins A and B (MICA/B), thus impairing NK cell activation. Shedding of these ligands is induced by endoplasmic reticulum protein 5-mediated cleavage by a disintegrin associated metalloproteinase (ADAM)10 or ADAM17 proteases, which are upregulated in cancers. The restoration of NK surveillance at least partly explains why inhibitors targeting these proteases have shown anti-cancer efficacy in preclinical studies. Impaired binding of perforin to the tumor cell surface can also prevent NK cell-mediated killing of cancer cells. Additionally, shedding of the target antigen can induce resistance to NK cell-based immunotherapies as is observed in the case of chimeric antigen receptor (CAR)-T cells. Other mechanisms of NK suppression include exhaustion due to prolonged NK cell hyperactivation. Such hyperactivation-induced NK cell exhaustion can be countered using checkpoint blockade.  

Finally, the above-described defective NK cell homeostasis can impact the anti-tumor immune surveillance by other immune cells. For example, migration of dendritic cells (DCs) to the tumor microenvironment (TME) is impacted when NK cells fail to produce chemokines, including C-C motif chemokine ligand 5 and X-C motif chemokine ligands 1 and 2 due to an increase in tumor-derived prostaglandin E2 (PGE2). Other studies have shown that the production of the Fms-like tyrosine kinase 3 ligand cytokine by NK cells positively regulates DC abundance in the TME, improves response to checkpoint blockade, and leads to improved overall survival. In a pancreatic ductal adenocarcinoma murine model, the Fms-like tyrosine kinase 3 ligand reduced frequencies of pathogenic Th17 cells and increased the numbers and effector functions of cytotoxic CD8+ T cells. Consequently, defective NK surveillance in cancers has far-reaching impacts on global anti-cancer host immunity.  

The increased suppression of NK surveillance at a higher stage of the cancer and size of the tumor strongly suggests that defects in NK cell-mediated immune surveillance of cancers are triggered by signaling mechanisms from within the tumor. For example, tumor-derived soluble factors such as PGE2, indoleamine 2,3-dioxygenase, transforming growth factor-beta (TGF-β), BCL-2 associated athanogene cochaperone 6, and programmed cell death protein ligand 1 bind to NK activating receptors, thereby blocking their target cell-binding site and tilting the balance towards NK cell inhibitory responses.  

Tumor-derived TGFβ1 downregulates Nkp30 and NKGD2D surface expression in human NK cells. Tryptophan catabolism mediated by indoleamine 2,3-dioxygenase inhibits the surface expression of Nkp46 and NKGD2D activating
receptors. In virus-induced cancers, viral factors such as EBV encoded microRNA-BART 2-5p, downregulate the NKG2D ligand MICB expression by binding to the 3′ untranslated region of MICB, thereby impairing NK cell-mediated clearance of EBV infected cells. The human papilloma virus encoded oncoproteins E6 and E7 inhibit IL-18 induced IFN-γ production in NK cells and contribute to immune escape of HPV or HPV-induced cervical cancer. Similarly, human T-cell leukemia virus, PGE2, and hepatitis A virus interfere with type-I interferon (IFN-I), which is an essential factor for NK cell homeostasis, activation, and anti-cancer functions.

Apart from the tumor secreteome, expression of ligands to NK checkpoint molecules including programmed cell death protein ligand 1 on cancer cells has been shown to promote NK cell exhaustion by binding to programmed cell death protein 1 (PD-1) on CD56bright CD16- NK cells. Other mechanisms of suppression include expression of CD39 on patient breast cancer cells that bind to tumor-infiltrating regulatory NK cells expressing CD73. CD73+ NK cells upregulate IL-10 production via signal transducer and activator of transcription-3, and thereby, suppress CD4+ T cell proliferation and IFN-γ production resulting in immune tolerance. Poliovirus receptor (CD155) is a common ligand for NK activation receptor DNAM-1 and inhibitory receptors T-cell immunoglobulin and ITIM domain (TIGIT) and CD96. CD155 interaction is known to be highly expressed in many human cancers while absent in most healthy tissues. CD155 expression on tumor cells downregulates DNAM-1 expression on NK cells and interferes with NK cell activation. Similarly, the human leukocyte antigen (HLA) class I histocompatibility antigen, alpha chain E (HLA-E), a ligand for CD94/NKG2A inhibitory receptor on NK cells, is highly expressed in tumors. NK cell recognition of HLA-E through CD94/NKG2A protects cancer cells from NK cell-mediated lysis. Studying the remodeling of the immune microenvironment during primary tumorigenesis in transgenic mouse models of cancer, we and the laboratories of other groups have shown that overexpression of universal tumor oncoproteins including, MYC and RAS lead to a reduction in NK cell numbers within the tumor microenvironment. In a MYC-driven T-cell lymphoblastic leukemia/lymphoma mouse model, we showed that tumor-intrinsic MYC inhibits the early development of NK cells in the bone marrow as well as the maturation of NK cells into cytotoxic effectors in the periphery by suppressing the transcription of a class of NK cell activating cytokines termed IFN-Is. In lung adenocarcinoma, MYC and RAS oncoproteins cooperate to drive the CCL9 and IL-23 mediated expulsion of B-, T- and NK cells. As in our T-ALL/lymphoma model after MYC in activation, deactivation of the driver oncogene MYC in lung adenocarcinoma induces NK cell-mediated tumor regression. The above studies confirm that tumor-driven signaling is the primary driver of NK cell suppression in cancers.

### Strategies to restore NK surveillance in cancer

The above outlined severe suppression of NK cells in cancer highlights the importance of developing strategies to restore anti-tumor NK surveillance (Fig. 1). One such strategy is to enhance the functions of the suppressed NK cells in the tumor microenvironment. NK cell functions can be enhanced by modulating the activity of activating and inhibitory receptors, blockade of immune checkpoints and exhaustion markers on NK cells using therapeutic antibodies, administering single and bi-specific antibodies to enhance the ADCC, and engineering NK cells to secrete NK cell growth-promoting cytokines.

Suppression of signaling from NK cell inhibitory receptors, which bind to tumor cells that have retained or upregulated their MHC-I, has been achieved by blocking the interaction between killer immunoglobulin like receptor and class-I MHC molecules. In preclinical studies, Irlimumab or IPH2101 human mAb that binds to the inhibitory receptors killer immunoglobulin-like receptor 2 immunoglobulin domains long cytoplasmic tail-1, -2, and -3 amplified NK cell-mediated cytolysis of HLA-C expressing tumor cells, including acute myeloid leukemia (AML) and multiple myeloma (MM) cells while sparing the normal peripheral blood mononuclear cells. Blocking of immune checkpoint molecules such as PD-1, TIGIT, and cytotoxic T lymphocyte associated protein-4 enhance NK cell-mediated tumor control by preventing NK cell exhaustion. Monoclonal antibodies such trastuzumab and rituximab, which target epidermal growth factor receptor and CD20, respectively, on tumor cells induce NK cell-mediated ADCC of tumor cells. The therapeutic efficacy of NK cells can be enhanced by co-administering anti-cancer, but NK cell growth-promoting, cytokines such as IL-2, IL-12, IL-15, IL-21, and Type I IFNs.

### Clinical relevance of developing NK cell-based therapies

Clinical development of NK cells was inspired by the ability of NK cells to exert the graft versus leukemia effect in HLA-mismatched hematopoietic stem cell transplants. The Ruggeri group demonstrated that allogeneic NK cells have the potential to eradicate leukemia and its relapse while at the same time protecting the patients from GVHD. Other groups showed that adoptive transfer of haploidential NK cells combined with a low dose of IL-2 after effective lymphodepletion chemotherapy in patients with AML resulted in increased endogenous IL-15 production that promoted persistence and expansion of NK cells. The fact that haploidentical NK cells can persist and expand in vivo further strengthens the notion that they can be used alone or as hematopoietic stem cell transplants to treat blood cancers.

Subsequently, the importance of NK cell-based therapies has been further underscored by numerous findings that an increased degree of NK cell infiltration in the TME, as well as high peripheral blood NK cell counts, predict favorable clinical prognosis. Most recently, we found in patients with high-risk B- and T-ALL that, the activation and maturation status of the NK cells in the leukemia microenvironment, rather than the number of NK cells, independently predicts clinical prognosis. Specifically, we observed that an increased relative frequency of activated but immature and dysfunctional NK cells is associated with worse prognosis in patients with ALL. Our findings further strengthen the premise for developing allogenic NK cell-based therapies for treating cancers instead of excessively engineering defective autologous NK cells.

### Advantages of NK cells over other forms of cell-based immunotherapies

Over the last decade, NK cell-based immunotherapies have gained attention as a safer and off-the-shelf alternative to autologous CAR-T cell-based therapies. This is because, unlike T cells, NK cell functions are not HLA-restricted, they do not exhibit cytokine release syndrome, and have less neurotoxicity than CAR-T cells. Most importantly, allogeneic NK cells do not cause GVHD and have, in fact, been shown to reduce GVHD while concurrently enhancing graft versus tumor effects. These advantages of NK cells have made them particularly attractive as alternatives for
CAR-T cell-based therapies and accelerated the development of CAR-NK cells, described below.

**NK cell-based therapies under clinical and pre-clinical development**

**Chimeric Antigen Receptor NK cells**

The design of CAR NK cells is adapted from the design of CAR-T cells, currently used for the treatment of cancers. A CAR consists of three domains: an ectodomain, a transmembrane domain, and a cytoplasmic activation domain. The ectodomain is a single-chain variable fragment (ScFv) that confers specificity. The ScFv is connected to a spacer (hinge) region to provide flexibility to the ScFv fragment. CAR spacers are mostly derived from IgG, CD8α, and CD28. The transmembrane domain links the ectodomain domain to the intracellular activation domain and anchors the receptor to cell membrane. The CD8α and CD28 based transmembrane domain are used in primary CAR-NK cells whereas CD28 is frequently used for CAR-NK-92 cell lines. The cytoplasmic activation domain, which transduces the signal in response to target antigen binding in CAR-NK cells, is the CD3 receptor ζ-chain. To potentiate intracellular signaling and CAR-NK activation, the signaling domain is often coupled with a co-stimulatory domain such as CD28, PD-1, 4-1BB, 4-1BB, DAP10, or DAP12.

CAR-NK cell-based therapies can be developed from NK cells derived from varied sources including peripheral blood (PB), cord blood (CB), induced pluripotent stem cells (iPSCs), and NK cell lines. NK cells from each source have their pros and cons.
to engineer using conventional lentiviral vector-based transduction methods to introduce the CAR vector. For this reason, a majority of the ongoing clinical trials have employed scalable NK cell lines such as the NK-92. However, cell lines such as NK-92 are malignant and have been derived from patients with NK cell neoplasms, thus requiring them to be irradiated before infusion. Such irradiation limits the in vivo persistence and effector functions of CAR-NK92 cells and calls for frequent infusions in a single patient. Contrary to PB and CB NK cells, iPSC-derived NK cells are homogenous and can be generated in larger quantities for off-the-shelf therapeutic applications.

**IL-15 expressing NK cells**

IL-15 is required for the development and function of NK cells. Mice deficient in the IL15 receptor alpha lack both functional T and NK cells in the spleen. Therefore, to support the long-term persistence and expansion of NK cells in vivo, NK cells have been engineered to express IL-15. CAR NK-92 cells engineered to express membrane-bound IL-15/IL-15 receptor alpha complex demonstrated superior proliferation under in vitro conditions. IL-15 CAR NK cells targeting epithelial cell adhesion molecule showed selective and increased cytolytic activity against NK-resistant epithelial cell adhesion molecule-expressing breast carcinoma cells. CB CD19-CAR-NK cells expressing IL-15 efficiently lysed primary B-ALL cells and cell lines in vitro and dramatically prolonged the survival of leukemia lymphoma-bearing mice. Ectopic expression of IL-15 in NKG2D CAR-NK cells restrained tumor growth and significantly enhanced survival of AML-bearing mice. However, a recent study showed that IL-15-secreting CAR-NK cells led to severe inflammation in AML-bearing mice due to the hyperproliferation of NK cells and high levels of proinflammatory cytokines. Hence, fine-tuning of IL-15-expressing CAR-NK cells to reduce its systemic toxicity is required.

**Gene-edited NK cell-based therapies**

The clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) gene-editing technology provides versatile and efficient gene manipulation capabilities to modulate various regulatory pathways in NK cells and fine-tune NK cell effector functions. Recently, Pomeroy et al., successfully knocked out ADAM17 and programmed cell death protein D1 genes in primary human NK cells by CRISPR/Cas9 methods and demonstrated that these genetically edited NK cells induced significantly more cytotoxicity of cancer cells as compared to their unmodified counterparts. Cas9-mediated promoter insertion to reactivate the silenced genes CD16 and DNAM-1 (CD226) in NK-92 cells significantly improved their cytotoxicity against cancer cell lines in vitro. Our group recently pioneered the generation of stable CRISPR/Cas9, dCas9-KRAB and dCas9-VP64 NK-92 cell line platforms that allow knockout, transcriptional repression, and transcriptional activation of genes, respectively, in NK cells. Our platforms can be seamlessly modified for off-the-shelf therapeutic applications. We predict that our CRISPR-engineered NK cell lines will allow the fine tuning of effector functions of NK cells while developing them as therapies.

**Combination of NK cells with other therapies, checkpoint inhibitors, and CAR-T cells**

The therapeutic benefits of combining NK cell monotherapy with other modalities of cancer treatment are currently being tested. For example, NK cells in conjunction with chemotherapy improved the clinical outcome in colon carcinoma patients. In preclinical studies, CAR-NK cells combined with a low dose of CAR-T cells delayed tumor progression and enhanced the survival of tumor bearing animals. In a gastric cancer mouse model, NK cells combined with anti-PD1 improved NK cell infiltration in the TME resulting in reduced tumor growth.

**Natural killer cell engagers**

As discussed previously, NK cells express a wide array of activation receptors, including CD16, signaling lymphocyte activation molecule family receptors, NKG2D, DNAM-1, and the natural cytotoxicity receptors Nkp30, Nkp44, and Nkp46. These receptors have been exploited in the clinic to induce ADCC using bis- and tri-specific Natural killer cell engagers (BiKe, TriKe). BiKe are constructed by joining ScFv targeting activation receptors on NK cells with an ScFv specific for a tumor antigen (BiKe) or two different tumor antigens (TriKe). The development of BiKe and TriKe for cancer treatment gained momentum after multiple studies demonstrated the effectiveness of bi-specific antibodies in engaging immune effector cells with tumor cells. Soon after, bi- and tri-specific antibodies were generated and tested in a wide range of tumors including non-Hodgkin’s lymphoma, mixed lineage leukemia, metastatic breast cancer, and ovarian cancers. The first clinical trial with NK cell activating bispecific monoclonal Ab (anti-CD16/CD30) was conducted in patients with refractory Hodgkin’s disease. A CD16×CD33 (1633) BiKe was tested in vitro using NK cells from patients with myelodysplastic syndromes to target CD33+ myeloid-derived suppressor cells (MDSCs). The CD16×CD33 BiKe not only reversed MDSC-driven immunosuppression of NK cells but also induced MDSC cell lysis. Subsequently, Vallera and colleagues introduced the IL-15 gene into the 1633 BiKe to make 161533 TriKe, which showed improved cytotoxicity, degranulation, and cytokine production against CD33+ human acute promyelocytic leukemia cell line, HL-60. More recently, the Vivier group developed a TriKe that targets two activation receptors, Nkp46 and CD16 on NK cells and a tumor antigen which exhibited superior killing potency as compared to BiKe in vitro.

**Challenges facing clinical use of NK cell-based therapies**

Although NK cell-based therapies are highly attractive, multiple challenges must be overcome before NK therapies can be taken into the clinic. Some of the major challenges in developing NK cells as therapies include difficulty in expanding NK cells ex vivo, reduced in vivo persistence of NK cells after infusion into the patients, functional impairment of NK cells once within the TME, resistance of tumor cells to NK cell-mediated lysis, difficulty in engineering NK cells to modify their functional properties, and limited infiltration of NK cells into solid tumors. To overcome these challenges, development of convenient and cost-effective protocols and workflows for ex vivo expansion and genetic engineering of NK cells is imperative, as is improvement of NK cell persistence in vivo.

**Future directions**

To facilitate ex vivo NK cell expansion for therapeutic appli-
tions, iPSC-derived NK cells are being employed because they are easier to scale up, undergo genetic modification, and provide sufficient supply of NK cells for use as allogeneic off-the-shelf immunotherapies. To improve NK cell persistence in vivo, we and others are engineering NK cells to express key cytokines required for their survival and proliferation.119,123 Other strategies include combining NK cells with agents that neutralize NK suppressive soluble factors such as TGF-β,119 or combining NK cells with agents that prevent shedding of NKG2D ligand by tumor cells and promote cytotoxicity of NK cell-based therapies in vivo.138 Strategies are being investigated to enhance NK cell infiltration into tumors by modifying chemokines and chemokine receptors on NK cells.138

Conclusions

Despite the roadblocks detailed earlier, the recent advances in developing NK cells for therapeutic applications are anticipated to accelerate the use of these therapies in the clinic in the near future.

Acknowledgments

Graphical art is created with the help of https://smart.servier.com/.

Funding

The following grants fund S. Swaminathan and her research: Translational Research Program Award from the Leukemia and Lymphoma Society (LLS 6624-21), Scholar Award from the American Society of Hematology, a Childhood Cancer Research Grant from the B+ Foundation, the P50 CA107399-12 National Cancer Institute Lymphoma SPORE Career Enhancement Program Pilot Award from the National Institutes of Health (PIs: Stephen J. Forman, Larry W. Kwak), and Research Start-Up from the Beckman Research Institute of City of Hope. A.K. and A.T.K. are funded by the above grants to S. Swaminathan.

Conflict of interest

Dr. Srividya Swaminathan has been an editorial board member of Exploratory Research and Hypothesis since November 2021. The authors have no other conflicts of interest to note.

Author contributions

Drafting of the manuscript (S.S.), critical revision of the manuscript for important intellectual content (A.K., A.T.K., S.S.), administrative, technical, or material support (S.S.), and study supervision (S.S.). All authors have made a significant contribution to this study and have approved the final manuscript.

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DOI: 10.14218/ERHM.2022.00024  |  Volume 00 Issue 00, Month Year
Kumar A, et al.: Natural killer cell-mediated immune surveillance in cancer

Explor Res Hypothesis Med


Kumar A. et al: Natural killer cell-mediated immune surveillance in cancer


