

Natural killer cell

Natural killer cells, also known as **NK cells** or **large granular lymphocytes (LGL)**, are a type of cytotoxic lymphocyte critical to the innate immune system. The role of NK cells is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response. NK cells provide rapid responses to virus-infected cells, acting at around 3 days after infection, and respond to tumor formation. Typically, immune cells detect the major histocompatibility complex (MHC) presented on infected cell surfaces, triggering cytokine release, causing the death of the infected cell by lysis or apoptosis. NK cells are unique, however, as they have the ability to recognize and kill stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction. They were named "natural killers" because of the initial notion that they do not require activation to kill cells that are missing "self" markers of MHC class 1.^[1] This role is especially important because harmful cells that are missing MHC I markers cannot be detected and destroyed by other immune cells, such as T lymphocyte cells.

NK cells (belonging to the group of innate lymphoid cells) are one of the three kinds of cells differentiated from the common lymphoid progenitor, the other two being B and T lymphocytes.^[2] NK cells are known to differentiate and mature in the bone marrow, lymph nodes, spleen, tonsils, and thymus, where they then enter into the circulation.^[3] NK cells differ from natural killer T cells (NKTs) phenotypically, by origin and by respective effector functions; often, NKT cell activity promotes NK cell activity by secreting interferon gamma. In contrast to NKT cells, NK cells do not express T-cell antigen receptors (TCR) or pan T marker CD3 or surface immunoglobulins (Ig) B cell receptors, but they usually express the surface markers CD16 (FcyRIII) and CD57 in humans, NK1.1 or NK1.2 in C57BL/6 mice. The NKp46 cell surface marker constitutes, at the moment, another NK cell marker of preference being expressed in both humans, several strains of mice (including BALB/c mice) and in three common monkey species.^{[4][5]}

In addition to the knowledge that natural killer cells are effectors of innate immunity, recent research has uncovered information on both activating and inhibitory NK cell receptors which play important functional roles, including self tolerance and the sustaining of NK cell activity. NK cells also play a role in the adaptive immune response.^[6] numerous experiments have demonstrated their ability to readily adjust to the immediate environment and formulate antigen-specific immunological memory, fundamental for responding to secondary infections with the same antigen.^[7] The role of NK cells in both the innate and adaptive immune responses is becoming increasingly important in research using NK cell activity as a potential cancer therapy.

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NK cell receptors

NK cell receptors can also be differentiated based on function. Natural cytotoxicity receptors directly induce apoptosis (cell death) after binding to Fas ligand that directly indicate infection of a cell. The MHC-independent receptors (described above) use an alternate pathway to induce apoptosis in infected cells. Natural killer cell activation is determined by the balance of inhibitory and activating receptor stimulation. For example, if the inhibitory receptor signaling is more prominent, then NK cell activity will be inhibited; similarly, if the activating signal is dominant, then NK cell activation will result.^[8]

NK cell receptor types (with inhibitory, as well as some activating members) are differentiated by structure, with a few examples to follow:

Activating receptors

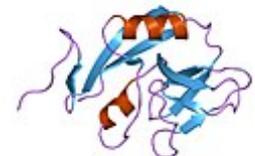
- **Ly49** (homodimers), relatively ancient, C-type lectin family receptors, are of multigenic presence in mice, while humans have only one pseudogenic Ly49, the receptor for classical (polymorphic) MHC I molecules.
- **NCR** (natural cytotoxicity receptors), a type of type 1 transmembrane proteins of the immunoglobulin superfamily, upon stimulation, mediate NK killing and release of IFN γ . They bind viral ligands such as hemagglutinins and hemagglutinin neuraminidases, some bacterial ligands and cellular ligands related to tumour growth such as PCNA.
- **CD16 (Fc γ IIIa)** plays a role in antibody-dependent cell-mediated cytotoxicity; in particular, they bind IgG.

Inhibitory receptors

- Killer-cell immunoglobulin-like receptors (KIRs) belong to a multigene family of more recently evolved Ig-like extracellular domain receptors; they are present in nonhuman primates, and are the main receptors for both classical MHC I (HLA-A, HLA-B, HLA-C) and nonclassical Mamu-G (HLA-G) in primates. Some KIRs are specific for certain HLA subtypes. Most KIRs are inhibitory and dominant. Regular



The HLA ligand for KIR



Protein structure of NKG2D



Protein structure of NKp44

cells express MHC class 1, so are recognised by KIR receptors and NK cell killing is inhibited.^[3]

- **CD94/NKG2** (heterodimers), a C-type lectin family receptor, is conserved in both rodents and primates and identifies nonclassical (also nonpolymorphic) MHC I molecules such as HLA-E. Expression of HLA-E at the cell surface is dependent on the presence of nonamer peptide epitope derived from the signal sequence of classical MHC class I molecules, which is generated by the sequential action of signal peptide peptidase and the proteasome. Though indirect, this is a way to survey the levels of classical (polymorphic) HLA molecules.
- **ILT** or **LIR** (immunoglobulin-like receptor) — are recently discovered members of the Ig receptor family.
- **Ly49** (homodimers) have both activating and inhibitory isoforms. They are highly polymorphic on the population level; though they are structurally unrelated to KIRs, they are the functional homologues of KIRs in mice, including the expression pattern. Ly49s are receptor for classical (polymorphic) MHC I molecules.

Function

Cytolytic granule mediated cell apoptosis

NK cells are cytotoxic; small granules in their cytoplasm contain proteins such as perforin and proteases known as granzymes. Upon release in close proximity to a cell slated for killing, perforin forms pores in the cell membrane of the target cell, creating an aqueous channel through which the granzymes and associated molecules can enter, inducing either apoptosis or osmotic cell lysis. The distinction between apoptosis and cell lysis is important in immunology: lysing a virus-infected cell could potentially release the virions, whereas apoptosis leads to destruction of the virus inside. α-defensins, antimicrobial molecules, are also secreted by NK cells, and directly kill bacteria by disrupting their cell walls in a manner analogous to that of neutrophils.^[3]

Antibody-dependent cell-mediated cytotoxicity

Infected cells are routinely opsonized with antibodies for detection by immune cells. Antibodies that bind to antigens can be recognised by FcγRIII (CD16) receptors expressed on NK cells, resulting in NK activation, release of cytolytic granules and consequent cell apoptosis. This is a major killing mechanism of some monoclonal antibodies like rituximab (Rituxan), ofatumumab (Azzera), and others. The contribution of antibody-dependent cell-mediated cytotoxicity to tumor cell killing can be measured with a specific test that uses NK-92, an immortal line of NK-like cells licensed to NantKwest, Inc. (<https://nantkwest.com>): the response of NK-92 cells (<https://nantkwest.com>) that have been transfected with a high-affinity Fc receptor are compared to that of the "wild type" NK-92 which does not express the Fc receptor.^[9]

Cytokine-induced NK and Cytotoxic T lymphocyte (CTL) activation

Cytokines play a crucial role in NK cell activation. As these are stress molecules released by cells upon viral infection, they serve to signal to the NK cell the presence of viral pathogens in the affected area. Cytokines involved in NK activation include IL-12, IL-15, IL-18, IL-2, and CCL5. NK cells are activated in response to interferons or macrophage-derived cytokines. They serve to contain viral infections while the adaptive immune response generates antigen-specific cytotoxic T cells that can clear the infection. NK cells work to control viral infections by secreting IFNγ and TNFα. IFNγ activates macrophages for phagocytosis and lysis, and TNFα acts to promote direct NK tumor cell killing. Patients deficient in NK cells prove to be highly susceptible to early phases of herpes virus infection.

Missing 'self' hypothesis

For NK cells to defend the body against viruses and other pathogens, they require mechanisms that enable the determination of whether a cell is infected or not. The exact mechanisms remain the subject of current investigation, but recognition of an "altered self" state is thought to be involved. To control their cytotoxic activity, NK cells possess two types of surface receptors: activating receptors and inhibitory receptors, including killer-cell immunoglobulin-like receptors. Most of these receptors are not unique to NK cells and can be present in some T cell subsets, as well.

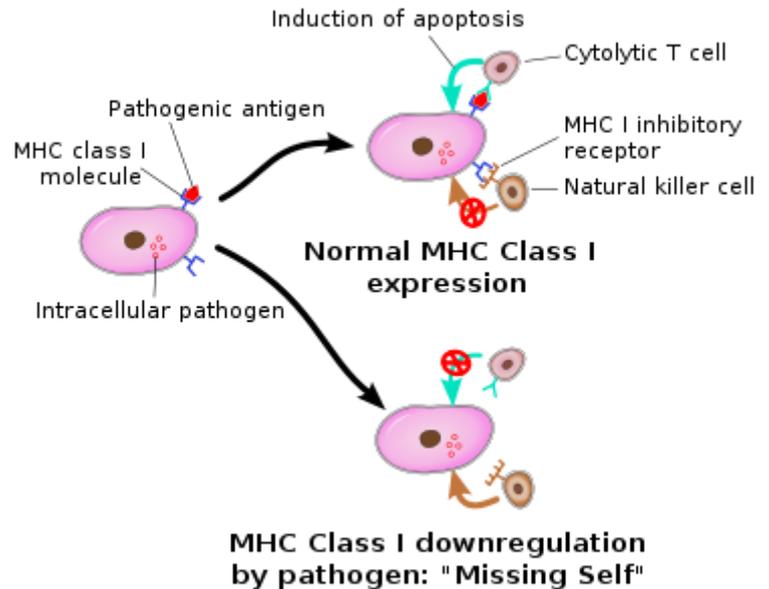
The inhibitory receptors recognize MHC class I alleles, which could explain why NK cells preferentially kill cells that possess low levels of MHC class I molecules. This mode of NK cell target interaction is known as "missing-self recognition", a term coined by Klas Kärre and co-workers in the late 90s. MHC class I molecules are the main

mechanism by which cells display viral or tumor antigens to cytotoxic T cells. A common evolutionary adaptation to this is seen in both intracellular microbes and tumors: the chronic down-regulation of MHC I molecules, which makes affected cells invisible to T cells, allowing them to evade T cell-mediated immunity. NK cells apparently evolved as an evolutionary response to this adaptation (the loss of the MHC eliminates CD4/CD8 action, so another immune cell evolved to fulfill the function).^[10]

Tumor cell surveillance

Natural killer cells often lack antigen-specific cell surface receptors, so are part of innate immunity, *i.e.* able to react immediately with no prior exposure to the pathogen. In both mice and humans, NKs can be seen to play a role in tumor immunosurveillance by directly inducing the death of tumor cells (NKs act as cytolytic effector lymphocytes), even in the absence of surface adhesion molecules and antigenic peptides. This role of NK cells is critical to immune success particularly because T cells are unable to recognize pathogens in the absence of surface antigens.^[1] Tumor cell detection results in activation of NK cells and consequent cytokine production and release.

If tumor cells do not cause inflammation, they will also be regarded as self and will not induce a T cell response. A number of cytokines are produced by NKs, including tumor necrosis factor α (TNF α), IFN γ , and interleukin (IL-10). TNF α and IL-10 act as proinflammatory and immunosuppressors, respectively. The activation of NK cells and subsequent production of cytolytic effector cells impacts macrophages, dendritic cells, and neutrophils, which subsequently enables antigen-specific T and B cell responses. Instead of acting via antigen-specific receptors, lysis of tumor cells by NK cells is mediated by alternative receptors, including NKG2D, NKp44, NKp46, NKp30, and DNAM.^[8] NKG2D is a disulfide-linked homodimer which recognizes a number of ligands, including ULBP and MICA, which are typically expressed on tumor cells. The role of dendritic cell—NK cell interface in immunobiology have been studied and defined as critical for the comprehension of the complex immune system.



Schematic diagram indicating the complementary activities of cytotoxic T cells and NK cells

NK cells, along with macrophages and several other cell types, express the Fc receptor (FcR) molecule (FC-gamma-RIII = CD16), an activating biochemical receptor that binds the Fc portion of IgG class antibodies. This allows NK cells to target cells against which a humoral response has been gone through and to lyse cells through antibody-dependant cytotoxicity (ADCC). This response depends on the affinity of the Fc receptor expressed on NK cells, which can have high, intermediate, and low affinity for the Fc portion of the antibody. This affinity is determined by the amino acid in position 158 of the protein, which can be phenylalanine (F allele) or valine (V allele). Individuals with high-affinity FcRgammaRIII (158 V/V allele) respond better to antibody therapy. This has been shown for lymphoma patients who received the antibody Rituxan. Patients who express the 158 V/V allele had a better antitumor response. Only 15–25% of the population expresses the 158 V/V allele. To determine the ADCC contribution of monoclonal antibodies, NK-92 cells (a "pure" NK cell line) has been transfected with the gene for the high-affinity FcR.

Adaptive features of NK cells—"memory-like", "adaptive" and memory NK cells

The ability to generate memory cells following a primary infection and the consequent rapid immune activation and response to succeeding infections by the same antigen is fundamental to the role that T and B cells play in the adaptive immune response. For many years, NK cells have been considered to be a part of the innate immune system. However, recently increasing evidence suggests that NK cells can display several features that are usually attributed to adaptive immune cells (e.g. T cell responses) such as dynamic expansion and contraction of subsets, increased longevity and a form of immunological memory, characterized by a more potent response upon secondary challenge with the same antigen.^{[11][12]} In mice, the majority of research was carried out with murine cytomegalovirus (MCMV) and in models of hapten-hypersensitivity reactions. Especially, in the MCMV model, protective memory functions of MCMV-induced NK cells were discovered^[13] and direct recognition of the MCMV-ligand m157 by the receptor Ly49 was demonstrated to be crucial for the generation of adaptive NK cell responses.^[13] In humans, most studies have focused on the expansion of an NK cell subset carrying the activating receptor NKG2C (KLRC2). Such expansions were observed primarily in response to human cytomegalovirus (HCMV),^[14] but also in other infections including Hantavirus, Chikungunya virus, HIV, or viral hepatitis. However, whether these virus infections trigger the expansion of adaptive NKG2C+ NK cells or whether other infections result in re-activation of latent HCMV (as suggested for hepatitis^[15]), remains a field of study. Notably, recent research suggests that adaptive NK cells can use the activating receptor NKG2C (KLRC2) to directly bind to human cytomegalovirus-derived peptide antigens and respond to peptide recognition with activation, expansion, and differentiation,^[16] a mechanism of responding to virus infections that was previously only known for T cells of the adaptive immune system.

NK cell function in pregnancy

As the majority of pregnancies involve two parents who are not tissue-matched, successful pregnancy requires the mother's immune system to be suppressed. NK cells are thought to be an important cell type in this process.^[17] These cells are known as "uterine NK cells" (uNK cells) and they differ from peripheral NK cells. They are in the CD56^{bright} NK cell subset, potent at cytokine secretion, but with low cytotoxic ability and relatively similar to peripheral CD56^{bright} NK cells, with a slightly different receptor profile.^[17] These uNK cells are the most abundant leukocytes present *in utero* in early pregnancy, representing about 70% of leukocytes here, but from where they originate remains controversial.^[18]

These NK cells have the ability to elicit cell cytotoxicity *in vitro*, but at a lower level than peripheral NK cells, despite containing perforin.^[19] Lack of cytotoxicity *in vivo* may be due to the presence of ligands for their inhibitory receptors. Trophoblast cells downregulate HLA-A and HLA-B to defend against cytotoxic T cell-mediated death. This would normally trigger NK cells by missing self recognition; however, these cells

survive. The selective retention of HLA-E (which is a ligand for NK cell inhibitory receptor NKG2A) and HLA-G (which is a ligand for NK cell inhibitory receptor KIR2DL4) by the trophoblast is thought to defend it against NK cell-mediated death.^[17]

Uterine NK cells have shown no significant difference in women with recurrent miscarriage compared with controls. However, higher peripheral NK cell percentages occur in women with recurrent miscarriages than in control groups.^[20]

NK cells secrete a high level of cytokines which help mediate their function. NK cells interact with HLA-C to produce cytokines necessary for trophoblastic proliferation. Some important cytokines they secrete include TNF- α , IL-10, IFN- γ , GM-CSF and TGF- β , among others.^[17] For example, IFN- γ dilates and thins the walls of maternal spiral arteries to enhance blood flow to the implantation site.^[21]

NK cell evasion by tumor cells

By shedding decoy NKG2D soluble ligands, tumor cells may avoid immune responses. These soluble NKG2D ligands bind to NK cell NKG2D receptors, activating a false NK response and consequently creating competition for the receptor site.^[1] This method of evasion occurs in prostate cancer. In addition, prostate cancer tumors can evade CD8 cell recognition due to their ability to downregulate expression of MHC class 1 molecules. This example of immune evasion actually highlights NK cells' importance in tumor surveillance and response, as CD8 cells can consequently only act on tumor cells in response to NK-initiated cytokine production (adaptive immune response).^[22]

History

In early experiments on cell-mediated cytotoxicity against tumor target cells, both in cancer patients and animal models, investigators consistently observed what was termed a "natural" reactivity; that is, a certain population of cells seemed to be able to lyse tumor cells without having been previously sensitized to them. The first published study to assert that untreated lymphoid cells were able to confer a natural immunity to tumors was performed by Dr. Henry Smith at the University of Leeds School of Medicine in 1966,^[23] leading to the conclusion that the "phenomenon appear[ed] to be an expression of defense mechanisms to tumor growth present in normal mice." Other researchers had also made similar observations, but as these discoveries were inconsistent with the established model at the time, many initially considered these observations to be artifacts.^[24]

By 1973, 'natural killing' activity was established across a wide variety of species, and the existence of a separate lineage of cells possessing this ability was postulated. The discovery that a unique type of lymphocyte was responsible for "natural" or spontaneous cytotoxicity was made in the early 1970s by doctoral student Rolf Kiessling and postdoctoral fellow Hugh Pross, in the mouse,^[25] and by Hugh Pross and doctoral student Mikael Jondal in the human.^{[26][27]} The mouse and human work was carried out under the supervision of professors Eva Klein and Hans Wigzell, respectively, of the Karolinska Institute, Stockholm. Kiessling's research involved the well-characterized ability of T lymphocytes to lyse tumor cells against which they had been previously immunized. Pross and Jondal were studying cell-mediated cytotoxicity in normal human blood and the effect of the removal of various receptor-bearing cells on this cytotoxicity. Later that same year, Ronald Herberman published similar data with respect to the unique nature of the mouse effector cell.^[28] The human data were confirmed, for the most part, by West et al.^[29] using similar techniques and the same erythroleukemic target cell line, K562. K562 is highly sensitive to lysis by human NK cells and, over the decades, the K562 ⁵¹chromium-release assay has become the most commonly used assay to detect human NK functional activity.^[30] Its almost universal use has meant that experimental data can be compared easily by different laboratories around the world.

Using discontinuous density centrifugation, and later monoclonal antibodies, natural killing ability was mapped to the subset of large, granular lymphocytes known today as NK cells. The demonstration that density gradient-isolated large granular lymphocytes were responsible for human NK activity, made by Timonen and Saksela in 1980,^[31] was the first time that NK cells had been visualized microscopically, and was a major breakthrough in the field.

New findings

Anticancer therapy

Since NK cells recognize target cells when they express nonself HLA antigens (but not self), autologous (patients' own) NK cell infusions have not shown any antitumor effects. Instead, investigators are working on using allogeneic cells from peripheral blood, which requires that all T cells be removed before infusion into the patients to remove the risk of graft versus host disease, which can be fatal. This can be achieved using an immunomagnetic column (CliniMACS). In addition, because of the limited number of NK cells in blood (only 10% of lymphocytes are NK cells), their number needs to be expanded in culture. This can take a few weeks and the yield is donor-dependent. A simpler way to obtain high numbers of pure NK cells is to expand NK-92 cells whose cells continuously grow in culture and can be expanded to clinical grade numbers in bags or bioreactors.^[32] Clinical studies have shown it to be well tolerated and some antitumor responses have been seen in patients with lung cancer, melanoma, and lymphoma.^{[33][34]} However, there are significant limitations associated with NK-92 immunotherapy, as the cell line was derived from a patient with non-Hodgkin lymphoma and thus must be irradiated prior to infusion, thus limiting persistence *in vivo*. Furthermore, NK-92 cells lack CD-16, making them unable to perform ADCC, preventing this therapy from being used in combination with monoclonal antibody therapies.^[35]

Infusions of T cells engineered to express a chimeric antigen receptor that recognizes an antigen molecule on leukemia cells could induce remissions in patients with advanced leukemia. Logistical challenges are present for expanding T cells and investigators are working on applying the same technology to peripheral blood NK cells and NK-92.

In a study at Boston Children's Hospital, in coordination with Dana-Farber Cancer Institute, in which immunocompromised mice had contracted lymphomas from EBV infection, an NK-activating receptor called NKG2D was fused with a stimulatory Fc portion of the EBV antibody. The NKG2D-Fc fusion proved capable of reducing tumor growth and prolonging survival of the recipients. In a transplantation model of LMP1-fueled lymphomas, the NKG2D-Fc fusion proved capable of reducing tumor growth and prolonging survival of the recipients.

In Hodgkin Lymphoma, in which the malignant Hodgkin Reed-Sternberg cells are typically HLA class I deficient, immune evasion is in part mediated by skewing towards an exhausted PD-1hi NK cell phenotype, and re-activation of these NK cells appears to be one mechanism of action induced by checkpoint-blockade.^[36]

Innate resistance to HIV

Recent research suggests specific KIR-MHC class I gene interactions might control innate genetic resistance to certain viral infections, including HIV and its consequent development of AIDS.^[3] Certain HLA allotypes have been found to determine the progression of HIV to AIDS; an example is the HLA-B57 and HLA-B27 alleles, which have been found to delay progression from HIV to AIDS. This is evident because patients expressing these HLA alleles are observed to have lower viral loads and a more gradual decline in CD4⁺ T

cells numbers. Despite considerable research and data collected measuring the genetic correlation of HLA alleles and KIR allotypes, a firm conclusion has not yet been drawn as to what combination provides decreased HIV and AIDS susceptibility.

NK cells can impose immune pressure on HIV, which had previously been described only for T cells and antibodies.^[37] HIV mutates to avoid NK cell activity.^[37]

Tissue-resident NK cells

Most of our current knowledge is derived from investigations of mouse splenic and human peripheral blood NK cells. However, in recent years tissue-resident NK cell populations have been described.^{[38][39]} These tissue-resident NK cells share transcriptional similarity to tissue-resident memory T cells described previously. However, tissue-resident NK cells are not necessarily of the memory phenotype, and in fact, majority of the tissue-resident NK cells functionally immature.^[40] These specialized NK-cell subsets can play a role in organ homeostasis. For example, NK cells are enriched in the human liver with a specific phenotype and take part in the control of liver fibrosis.^{[41][42]} Tissue-resident NK cells have also been identified in sites like bone marrow, spleen and more recently, in lung, intestines and lymph nodes. In these sites, tissue-resident NK cells may act as reservoir for maintaining immature NK cells in humans throughout life.^[40]

See also

- [Active hexose correlated compound](#)
- [Granzymes](#)
- [Hematopoiesis](#)
- [Immune system](#)
- [Interleukin](#)
- [Lymphatic system](#)

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Further reading

- *Cellular and Molecular Immunology* by Abbul K. Abbas & Andrew Lichtman Saunders Copyright 2003
- *How the Immune System Works*, 2nd edition, by Lauren Sompayrac, PhD Blackwell Publishing 2003
- *Immunobiology: The Immune System In Health And Disease* by Janeway, Travers, Walport & Shlomchik Churchill Livingstone Copyright 2005
- *Kuby Immunology*, 6th edition, by Thomas J. Kindt, Richard A. Goldsby, and Barbara A. Osborne, W.H. Freeman and Company, New York

External links

- Video of natural killer cell (<https://www.youtube.com/watch?v=HNP1EAYLhOs>)

- [CopeWithCytokines Portal to definitions of NK-Cells and closely related topics \(http://www.copewithcytokines.de/cope.cgi?key=NK-cells\)](http://www.copewithcytokines.de/cope.cgi?key=NK-cells)
- <https://web.archive.org/web/20100122025038/http://www.hfea.gov.uk/fertility-treatment-options-reproductive-immunology.html> Reproductive immunology and fertility treatment
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- [Natural+Killer+Cells \(https://meshb.nlm.nih.gov/record/ui?name=Natural%20Killer%20Cells\)](https://meshb.nlm.nih.gov/record/ui?name=Natural%20Killer%20Cells) at the US National Library of Medicine [Medical Subject Headings \(MeSH\)](#)
- [Nkcells.info \(https://web.archive.org/web/20180921143231/http://nkcells.info/\)](https://web.archive.org/web/20180921143231/http://nkcells.info/) - MediaWiki-based information platform specializing on natural killer cells
- [Large granular lymphocyte \(http://www.cancer.gov/dictionary?Cdrid=44440\)](http://www.cancer.gov/dictionary?Cdrid=44440) entry in the public domain NCI Dictionary of

Cancer Terms

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