Review Article

Natural Killer Cells in Health and Disease: Mechanisms of Dysfunction and Emerging Therapeutic Targets

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ABSTRACT

Natural Killer (NK) cells are a key component of the innate immune system, responsible for the rapid detection and elimination of virally infected and malignant cells. As our knowledge of immune cells including NK cells continues to expand, recent research revealed a complex network of intrinsic and extrinsic factors that modulate NK cell function in both health and disease. This review explores diverse pathological contexts in which NK cell activity is impaired, including severe viral infections (e.g., COVID-19), cancers such as multiple myeloma, immune evasion via checkpoint molecules like IGSF8, and the stage of immunosenescence due to aging. We also highlight metabolic exhaustion observed in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) and novel epigenetic suppression mechanisms mediated by the SUPT16H–BRD4 axis. Transcriptional regulators T-BET and EOMES are shown to be indispensable for maintaining NK cell identity and cytotoxic integrity. Through these case studies, we identify shared patterns of dysfunction, such as impaired cytokine signaling, defective immune synapse formation, and energy metabolism failure, and discuss the emerging therapeutic strategies aimed at reversing them. A comprehensive list of molecular markers discussed across these cases is provided in Supplementary Table 1. Together, these findings emphasize the critical role of NK cells in immune surveillance and emphasize their potential as targets for innovative immunotherapies in infection, cancer, and chronic immune disorders.

Keywords: Natural killer cells; cytotoxicity; innate lymphoid cells, immunosenescence

INTRODUCTION

Natural Killer (NK) cells form an integral component of the immune response to maintain health and defend against virally infected cells and cancer cells (1). As a granular lymphocyte, NK cells are especially specialized in identifying and destroying these abnormal cells. Their identification begins with Major Histocompatibility Complex 1 (MHC-1) (Figure 1).

When a cell becomes infected by a virus or turns cancerous, it loses its expression of MHC class I. Without this key signal marker, the inhibitory receptors on NK cells remain inactive. As a result, NK cells shift into cytotoxic action, recognizing the abnormal cell as a threat and releasing toxic molecules to destroy it. Two

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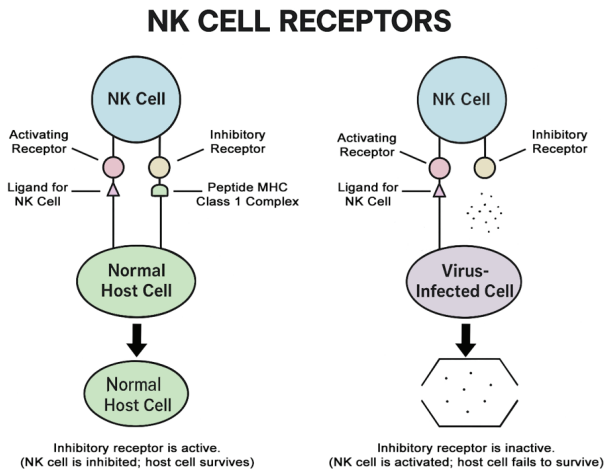

Figure 1. Mechanism of NK cell recognition of normal and virally infected cell using peptide MHC class 1 complex. In normal host cells, MHC1 is expressed and successfully binds to the inhibitory receptor of NK cell, suppressing its destructive feature and allowing the host cell to survive. Created using Adobe Photoshop.

key molecules released during this process are perforin and granzyme (2). Perforin forms pores in the target cell's membrane, creating entry points for other immune cells for easier destruction, while granzyme enters through these pores and triggers apoptosis.

Promptly following the release of perforin and granzyme, various immune cells such as activated T cells, macrophages, monocytes, dendritic cells, endothelial cells and even NK cell themselves, begin to secrete interleukins, which is a group of cytokines to help coordinate and amplify immune response. These interleukins promote the activation, communication, and proliferation of immune cells, ultimately aiding the body's defense against these abnormal cells.

A range of NK cell markers relevant to cytotoxicity, exhaustion, and immune evasion are discussed in this study. A complete summary is provided in Supplementary Table 1.

Interaction of Perforin and IL-6, in the case of severe viral infection, Covid-19

Coronavirus disease of year 2019 (COVID-19) is a highly infectious viral infection of SARS-coronavirus-2 (SARS-CoV-2) with serious morbidity and mortality rate (4). As COVID-19 critically struck vulnerable populations with adverse risk factors including obesity, heart disease, diabetes, and higher age, these groups also expressed significantly lower level of perforin (5). Infections that would have been normally tolerated by perforin and granzyme produced by NK cells and T cells were not tolerated by these population with underlying conditions due to their low perforin levels or exhausted NK cells. Infections are cleared at a much slower rate causing a prolonged immune activation leading to a cytokine storm.

Immune system in the effort of controlling the infection, starts to produce high levels of IL-6, which is a cytokine that amplifies immune response during an infection. As the monocytes and macrophages continuously produce high level of IL-6 triggering immune response such as inflammation, fever, tissue damage, even more immune response is triggered causing a positive feedback loop of IL-6 secretion. As IL-6 suppresses perforin, NK cells become less effective, and reduced performance of NK cell triggers more activation of neutrophils leading to increased inflammation, worsening the situation even more (Table 1).

This cycle highlights the critical role of NK cells in maintaining immune balance during such viral infections. When NK cell function is compromised due to low perforin levels or cytokine induced suppression, the immune system starts harming itself through an overactivation and uncontrolled inflammation. As can be seen in this study, NK cells in antiviral defense system is highly important and suggest their potential as therapeutic targets in treating immune dysregulation in forementioned vulnerable population with underlying health conditions.

NK cell impairment in multiple myeloma cases

Similar to the perforin deficiency in severe viral infections like COVID-19, another prominent example of dysfunctional NK cell response can be observed in multiple myeloma (MM), a cancer of plasma cells where NK cells exhibit impaired adhesion, signaling, and cytotoxicity despite their increased numbers.

In MM patients, NK cells are not necessarily reduced in number but instead exhibit some critical functional impairments. Specifically, researchers have identified an expanded population of $CD16^{low}/CD226^{low}$ NK cells that lack essential cytotoxic abilities (6). These cells display diminished perforin and granzyme expression, produce lower levels of IFN-γ, and show reduced CD107a surface mobilization, a marker of degranulation. Despite the completion of maturation process, these NK cells are unable to effectively adhere to or kill tumor cells.

This dysfunction stems from defects in immune synapse formation. Blanquart lab discovered that NK

Table 1. Overview of interleukin origin, target and function in immune response

Interleukin	Secreted by	Targets	Purpose
IL-1	Macrophage, Lymphocyte, Endothelium, Fibroblast, Astrocyte	Various immune cells, including T-cells and endothelial cells	Promote inflammation during cell death through lymphocyte activation and leukocyte-endothelial cell adhesion
IL-2	T cell	T cells, NK cells	T cell growth factor and activates NK cell
IL-3	T cell	Multipotent hematopoietic stem cells	Supports growth and differentiation of stem cells into various blood cells
IL-4	T cell	B cells, T cells, mast cells	Promotes B-cell differentiation and antibody production
IL-5	T cell	B cells, eosinophils	Stimulates growth and differentiation of B cells and eosinophils
IL-6	T cells, B-cells, monocytes, macrophages, fibroblasts	Liver, T cells, B cells, hepatocytes	Amplifies immune response during infection and inflammation
IL-7	Lymphocyte	Progenitor T and B cells	Supports lymphocyte development and survival
IL-8	T cells, macrophages	Neutrophil	Attracts and activates neutrophils
IL-9	T cell	T cells, mast cells	Supports T-cell proliferation and mast cell function
IL-10	T cell	Macrophages, dendritic cells	Anti-inflammatory; suppresses immune response
IL-11	Bone marrow stromal cells	Megakaryocytes	Stimulates platelet production
IL-12	macrophage	NK cells, T cell	Activates NK cells and promote immune response

This table summarizes key interleukins involved in immune regulation starting with their sources, target cells or tissues and their purposes. Interleukins are a subset of cytokines that are often recruited following the activation of NK cells. These act as signaling molecules to coordinate communication between immune cells during inflammatory processes (3).

cells in MM show impaired LFA-1 opening, a molecule essential for binding to target cells, and have difficulty assembling the actin cytoskeletal ring required for targeted cytolysis. As a result, their interactions with tumor cells are ineffective, allowing malignant cells to evade immune surveillance.

Clinically, the presence of this CD16/CD226^{low} NK cell phenotype has been associated with poorer overall survival, even in patients classified as low-risk based on cytogenetics. This finding highlights the importance of NK cell quality beyond simple quantity of NK cells. More importantly, current immunotherapies such as anti-CD38 monoclonal antibodies rely on Fc receptor (CD16) engagement. In patients with downregulated CD16 expression, such therapies may be less effective, emphasizing a critical need to restore NK cell function, not merely just increasing their count.

This case demonstrates that NK cell impairment in cancer is multifaceted, involving both intrinsic signaling deficits and external suppression within the tumor microenvironment, requiring therapeutic strategies that go beyond boosting cell counts.

NK cell dysfunction and role of IGSF8 in immune evasion

As reviewed above, NK cell cytotoxicity plays a critical role in identifying and eliminating malignant. However, few cases discussed in previous sections also reviewed how NK cell function can be impaired due to intrinsic defects or overactivation. Then how can we accurately assess NK cell dysfunction and identify biomarkers when NK cells are suspected to play a role in a disease?

Recent study has identified IGSF8 as a novel immune checkpoint molecule that regulates NK cell activity and may serve as both a diagnostic marker and a promising target for cancer immunotherapy (7). IGSF8 is a

transmembrane protein that becomes overexpressed in certain cancer cells. In tumors where MHC-1 is lost, IGSF8 is capable of overriding this absence by binding to inhibitory receptor KIR3DL2 on NK cells. This binding suppresses NK cell degranulation and reduces cytotoxic activity, allowing the tumor to evade immune surveillance and form "immune cold" tumors.

In response to this finding, Li lab developed IGSF8.06, an antibody of IGSF8, that targets and blocks IGSF8. This antibody restores NK cell toxicity and produce a synergic effect when combined with other immunotherapies such as anti-PD1 by enhancing both NK cell and T cell activation. While anti-IGSF8 alone has shown moderate efficacy in inhibiting tumor growth, therapy combined with anti-PD1 significantly amplified the anti-tumor response.

This discovery not only provides insight into why NK cells sometimes fail to eliminate MHC-I deficient tumors, but also introduces a novel pathway by which cancer cells evade immune destruction.

Immunosenescence of NK cells: evaluation in Chinese healthy adults

NK cells are not immune to the gradual decline of immune competence that comes with aging. While many immune cell types decline in number or diversity with age, NK cells exhibit a paradoxical pattern. A large-scale immunological analysis of over 43,000 healthy Chinese adults revealed a distinct age-associated remodeling of NK cell populations (8). Although the relative percentage of NK cells and particularly the $CD56^+$ subsets increase notably after the age of 55, their absolute numbers remain stable, suggesting a compensatory redistribution instead of an increase in their number.

This increase in frequency, however, does not reflect improvements in its functionality. Hallmark sings of immunosenescence accompanies this increase including reduced proliferative capacity, altered cytokine responses, and impaired cytotoxic function. The study by Jia *et al*., further showed that aging correlates with the loss of naïve $CD8^+$ T cells and γδ T cells, alongside a rise in terminally differentiated T cells, an immune landscape increasingly dominated by cells that are metabolically and functionally exhausted.

Using machine learning models, the researchers constructed an "immune age" index that often diverged from chronological age, particularly in individuals with chronic diseases. NK cell proportions were among the key predictors of immune aging, underscoring their dual role as effectors and biomarkers. This finding highlights a critical nuance: while aged individuals may exhibit higher frequencies of NK cells, their immune system's actual capacity to clear infections or tumor cells may be significantly compromised.

Jia *et al*., introduces another NK cell dysfunction beyond infection or other defects by introducing age as a substantial distortion in NK cell biology.

Transcriptional dysregulation in NK cells: the role of T-BET and EOMES

While external factors such as abnormal production of cytokine or tumor-mediated suppression can impair NK cell function, intrinsic regulatory mechanisms are equally essential in maintaining their cytotoxic capacity. Two transcription factors, T-BET (TBX21) and EOMES, are known to guide NK cell development, but recent findings demonstrate that they are also critical for sustaining the identity and function of mature NK cells (9).

In a study by Klose *et al*., deletion of both T-BET and EOMES in mature human NK cells resulted in severe impairment of their antitumor response, despite its sustained short-term killing abilities (10). These double-knockout NK cells showed marked reduction in IFN-γ, TNF production, and diminished expression of perforin and granzyme B, reflecting a collapse of key effector functions. Moreover, transcriptional and chromatin accessibility analyses revealed that the loss of T-BET and EOMES led to downregulation of NK-specific gene programs and the reproduction of an ILC3-like precursor phenotype.

Functionally, these NK cells became less responsive to critical activating signals such as IL-15 and IL-12, due to impaired signaling through pathways like STAT, AKT, and ERK. These results highlight that T-BET and EOMES are not merely involved in NK cell development, but are continuously required to preserve their cytotoxic identity, metabolic fitness, and responsiveness to cytokine stimulation.

This insight suggests that transcriptional regulation is a vital internal checkpoint for NK cell stability and should be considered when designing long-term NK cell–based immunotherapies.

Metabolic Dysregulation and Functional Exhaustion of NK Cells in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

While NK cell dysfunction has been studied extensively in the context of infection and cancer, recent research has also uncovered significant impairment in NK cell activity in patients with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS), which is a chronic,

multisystem disease often triggered by viral infections. NK cells, which serve as a front-line defense in the innate immune system, show markedly reduced cytotoxicity in ME/CFS patients despite being present in normal or near-normal numbers (11).

Frutoso Mortier lab suggests metabolic dysregulation as a key contributor to this dysfunction. In healthy individuals, NK cell activation through cytokines like IL-2 or IL-15 triggers a shift toward increased glycolysis and oxidative phosphorylation (OXPHOS) to meet its energetic demands. However, NK cells from ME/CFS patients exhibit impaired glycolytic capacity, suggesting a compromised ability to rapidly mobilize energy for cytotoxic responses. Interestingly, these cells show a compensatory upregulation in fatty acid oxidation (FAO), a metabolic shift that may indicate cellular stress but is insufficient for sustaining effective immune responses.

Functionally, ME/CFS associated NK cells demonstrate reduced expression of key cytolytic molecules such as perforin and granzyme B, and are less effective in clearing virus-infected or transformed cells. While these abnormalities suggest features of immune exhaustion, they do not fully align with conventional exhaustion phenotypes seen in chronic infections or cancer, as markers like GLUT1 remain unaffected. Frutoso Mortier lab's data points to a distinct form of metabolic exhaustion, which may represent a unique immune landscape in ME/CFS patients.

This case further explores NK cell dysfunction by introducing a non-malignant, non-infectious disease state where metabolism centered dysfunction plays a central role, offering critical insights into the complexity of NK cell regulation and its role in chronic immune mediated disorders.

Silencing of Interferon Signaling in NK Cells: The SUPT16H–BRD4 Axis

In addition to transcription factor dependent mechanisms, recent findings reveal that epigenetic regulation also plays a critical role in modulating NK cell cytotoxicity (12). Zhou lab focused on the FACT complex subunit SUPT16H, which demonstrated that its acetylation at lysine 674 by TIP60 promotes interaction with the BRD4 protein. This interaction stabilizes SUPT16H and forms a repressive complex that associates with epigenetic silencing enzymes such as HDAC1 and EZH2.

This SUPT16H–BRD4 complex effectively suppresses the expression of interferons, including both IFN-α and IFN-γ, by reducing histone acetylation and enhancing chromatin repression at interferon stimulated gene loci. In NK cells, this suppression translates into reduced cytokine secretion and impaired cytotoxic function.

However, when SUPT16H was inhibited pharmacologically using CBL0137, or silenced via RNA interference, NK cell activity was significantly restored. Treated NK cells exhibited enhanced IFN production and increased degranulation capacity. More importantly, these activated NK cells showed improved cytotoxicity against virus-infected targets, including Zika virus, Influenza A, and SARS-CoV-2.

This study reveals an epigenetic checkpoint of NK cell that can silence antiviral and cytotoxic programs. By targeting this pathway, it may be possible to reinvigorate NK cells in both infectious and malignant contexts where epigenetic repression diminishes immune defense.

CONCLUSION

Natural Killer (NK) cells emerge as central sentinels of immune surveillance, with dysfunction spanning a wide spectrum of diseases including viral infections, malignancies, chronic immune disorders, and age-related immunosenescence. Across these contexts, common mechanisms of impairment converge on defective cytokine signaling (e.g., IL-6-driven suppression), reduced expression or mobilization of cytotoxic granules (perforin and granzyme), metabolic exhaustion (as in ME/CFS), and inhibitory checkpoint engagement such as IGSF8–KIR3DL2 interactions. Epigenetic silencing through the SUPT16H–BRD4 axis and transcriptional dysregulation of T-BET and EOMES further highlight how both external and intrinsic pathways can compromise NK cell cytotoxic integrity.

From a therapeutic perspective, these insights underscore the potential of NK cell–based immunotherapies that extend beyond traditional strategies. Approaches such as checkpoint blockade (e.g., anti-IGSF8), metabolic reprogramming to restore glycolysis and OXPHOS, epigenetic modulators targeting chromatin repression, and genetic engineering to enhance persistence and activation of NK cells are emerging as promising interventions. Moreover, the combination of NK cell therapies with other immunotherapeutic modalities, including T cell checkpoint inhibitors (e.g., anti-PD1), holds potential for synergistic anti-tumor and anti-viral efficacy.

Future research must focus on integrating single-cell transcriptomics, metabolic profiling, and epigenetic mapping to develop precise biomarkers of NK cell health

and dysfunction. Personalized NK-based therapies, including adaptive NK cell transfer or CAR-NK technologies, could offer durable solutions for cancer, chronic infections, and immune-mediated syndromes. The ultimate challenge lies in overcoming tumor and viral immune evasion while ensuring the long-term safety and functional stability of NK cells *in vivo*.

LIMITATIONS

Despite the comprehensive scope of this review, several limitations should be considered before interpreting the findings. NK cell dysfunction across diseases is drawn from studies using different experimental models, including in vitro systems, murine models, and clinical patient samples. This variance in data may limit the direct comparability of findings and the generalizability of conclusions.

Furthermore, although individual studies provide insights into molecular markers such as CD16, T-BET, or IGSF8, many of these findings have yet to be validated across large patient populations or in diverse genetic and environmental backgrounds. The clinical utility of these proposed biomarkers remains under investigation. While the review highlights several potential therapeutic targets such as checkpoint inhibitors, metabolic reprogramming, and epigenetic modulation, many of these approaches are still in preclinical or early clinical phases. As a result, their long-term safety and feasibility requires further investigation for validation.

In summary, although the selected cases illustrate key dysfunction patterns and therapeutic possibilities, further longitudinal, mechanistic, and translational research is essential to fully characterize NK cell biology and optimize its clinical applications.

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SUPPLEMENTARY DATA

Supplementary Table 1. Comprehensive overview of molecular markers discussed throughout the manuscript, including their classification, function in NK cell biology, and disease-specific relevance

Marker	Type	Function in NK cells	Relevant Context
Perforin	Cytotoxic effector	Forms pores in target cell membranes to deliver granzymes	Suppressed in severe COVID-19, leading to delayed viral clearance
Granzyme B	Cytotoxic effector	Induces apoptosis in target cells after entry through perforin pores	Reduced in cancer and aging; essential for NK cytotoxicity
CD107a	Degranulation marker	Indicates NK cell degranulation and activation	Assessed in functional assays to evaluate NK activity
CD16 (FcγRIII)	Surface receptor	Mediates antibody-dependent cellular cytotoxicity (ADCC)	Downregulated in MM and ME/CFS; reduces ADCC capacity
CD226 (DNAM-1)	Activating receptor	Co-stimulatory receptor important for NK activation	Low in dysfunctional NK cells in multiple myeloma
LFA-1	Adhesion molecule	Required for immune synapse formation and target binding	Defective in MM; leads to poor synapse formation
KIR3DL2	Inhibitory receptor	Interacts with IGSF8 to suppress NK cell cytotoxicity	Engages IGSF8; involved in immune evasion by tumors
IGSF8	Checkpoint ligand	Immune checkpoint ligand overexpressed in tumors to evade NK attack	Overexpressed in cancer to block NK activity
T-BET (TBX21)	Transcription factor	Essential for NK cell development and effector function	Loss results in cytokine deficiency and identity loss
EOMES	Transcription factor	Maintains NK identity and cytotoxic profile	Loss shifts NK cells to ILC3-like progenitor state
IFN-γ	Cytokine	Activates immune cells and amplifies NK responses	Reduced in ME/CFS and Double Knock Out cells; impairs immunity
TNF	Cytokine	Mediates inflammation and supports NK antitumor functions	Diminished in aging and exhaustion; marker of dysfunction
CD56	Surface marker	Defines NK cell maturity and functional subsets (bright/dim)	Elevated in elderly; used in immune aging modeling
SUPT16H	Transcriptional suppressor	Suppresses IFN signaling and dampens NK cytotoxicity	Targets IFN gene repression; active in infection/cancer
BRD4	Chromatin reader	Stabilizes SUPT16H, enabling epigenetic repression	Binds acetylated SUPT16H; forms repressive chromatin complex
HDAC1	Histone deacetylase	Suppresses gene transcription through histone deacetylation	Silences cytokine and cytotoxic genes in NK cells
EZH2	Histone methyltransferase	Methylates histones, repressing transcription of NK genes	Represses effector function genes like PRF1, IFNG
GLUT1	Metabolic transporter	Regulates glucose uptake; altered in exhausted NK cells	Unaffected in ME/CFS despite exhaustion-like phenotype
mTORC1	Nutrient sensing pathway	Controls energy metabolism; downregulation linked to dysfunction	Inhibited in ME/CFS; linked to metabolic dysfunction

Continued Supplementary Table 1. Comprehensive overview of molecular markers discussed throughout the manuscript, including their classification, function in NK cell biology, and disease-specific relevance

Marker	Type	Function in NK cells	Relevant Context
PD-1	Inhibitory receptor	Exhaustion marker; may increase with chronic stimulation	Examined in aging; not elevated despite immune changes
γδ T cells	T cell subset	Decline with age; associated with impaired immune responses	Decline contributes to weakened immune diversity
Naïve CD8+ T cells	T cell subset	Decline with age; predictive of immune aging	Decline associated with immune senescence index
CD28	Co-stimulatory receptor	Loss correlates with immune senescence and poor T/NK function	Marker of T cell activation and functional capacity
CD62L	Lymph node homing receptor	Supports migration and long-term survival of NK cells	Facilitates NK homing and memory-like persistence

This table summarizes key surface receptors, transcription factors, effector molecules, cytokines, and metabolic regulators that are associated with NK cell function, dysfunction, or regulation in various pathological contexts such as infection, cancer, aging, and chronic immune conditions.