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Advancing natural killer cells as a next generation cancer immunotherapy

Abstract

Natural killer (NK) cells are innate lymphocytes capable of detecting and killing transformed cells independently of prior antigen exposure, rendering them an increasingly attractive platform for cancer immunotherapy. Recent advances have expanded NK-cell–based strategies from cytokine stimulation and antibody-mediated activation to adoptive transfer of allogeneic NK cells and sophisticated genetic engineering approaches. Early-phase clinical trials demonstrate that chimeric antigen receptor (CAR)-NK cells offer potent antitumor activity with favorable safety profiles, including minimal cytokine release syndrome and graft-versus-host disease. Current developments focus on enhancing NK-cell persistence, overcoming exhaustion, and improving resistance to the suppressive tumor microenvironment through precision gene editing, cytokine support, and next-generation NK-cell engagers. Collectively, these innovations position NK cells as a scalable, off-the-shelf immunotherapy platform with growing promise spanning both hematologic and solid tumors.

Keywords: natural killer cells, immunotherapy, oncolytic viruses, multiple clinical trial

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Joseph F Murphy
ImmunePCS LLC, USA

Correspondence: Joseph F Murphy, ImmunePCS LLC, Boston, MA 02169, USA, Tel +1 617 657-3320

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Introduction

NK cells are lymphocytes derived from the same lineage as B and T cells, but as components of the innate immune system they are classified as innate lymphoid cells (ILCs). In humans, NK cells typically represent a minority subset of circulating lymphocytes, generally falling within the 5–20% range. Their name reflects their defining feature: the ability to recognize and eliminate target cells without prior sensitization. NK cells play a central role in early immune defense and in maintaining immunological homeostasis. While they are best known for eliminating virally infected cells, they also contribute to tumor surveillance by detecting and responding to early signs of cellular transformation. Within solid tumors, NK cells must operate in the hypoxic and immunosuppressive conditions of the tumor microenvironment (TME). A defining feature of NK cells is their ability to detect and eliminate stressed or transformed cells without relying on classical MHC-restricted antigen presentation.[1]

NK-cell activity depends on the integration of signals from both activating and inhibitory receptors that survey cellular health, such as NKG2D, NKp30, NKp46, and DNAM-1, and inhibitory receptors including KIRs and NKG2A, which survey MHC class I expression on potential target cells. This receptor architecture enables NK cells to sense cellular stress signals, including oncogenic transformation, DNA damage, and viral infection, without requiring prior antigen priming.[2]

The tumor microenvironment imposes multiple metabolic and immunologic constraints-such as hypoxia, nutrient depletion, lactate buildup, adenosine, and TGF-β-that progressively weaken NK-cell effector function. Despite these challenges, NK cells can still recognize stress-induced ligands such as MICA/B and ULBPs, allowing them to eliminate tumor cells that escape T-cell surveillance by downregulating MHC class I.[3]

Discussion

Adoptive cellular immunotherapy seeks to restore or augment immune effector function in cancer patients. NK cells are particularly attractive for this purpose because they do not cause graft-versus-host disease (GVHD), rendering allogeneic therapy feasible and scalable. Early clinical trials using unmodified NK cells demonstrated both safety and biological activity. In a landmark study, haploidentical NK cells induced complete remission in 26% of patients with refractory acute myeloid leukemia (AML).[4] Also, in subsequent trials using umbilical cord blood NK cells showed *in vivo* expansion and measurable antitumor activity.[5] These foundational studies established that NK-cell infusions are safe, well tolerated, and capable of mediating clinical responses, paving the way for more sophisticated engineering strategies.

The success of chimeric antigen receptor (CAR)-T cells in hematologic malignancies catalyzed interest in (CAR)-engineered NK (CAR-NK) cells. Unlike CAR-T cells, which can trigger severe cytokine release syndrome (CRS) and neurotoxicity, CAR-NK cells have a more controlled cytokine profile and shorter lifespan, reducing the risk of life-threatening inflammation. They also retain their natural cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC), giving them multiple mechanisms to eliminate tumor cells.

A pivotal early-phase study evaluating cord-blood–derived CD19-CAR NK cells in relapsed or refractory lymphoid malignancies reported encouraging activity, with most patients responding and a majority achieving complete remission. Notably, no cases of CRS, neurotoxicity, or GVHD were observed, and engineered NK cells persisted for months after infusion. These outcomes demonstrated that CAR-NK cells can achieve potent antitumor activity with a dramatically improved safety profile compared to CAR-T therapy.[6]

Multiple next-generation CAR-NK platforms are now in clinical development, including:

I. FT596 (induced pluripotent stem cell (iPSC)-derived CAR-NK with IL-15 and CD16 engineering)

II. NKX101 (NKG2D-CAR-NK for AML and solid tumors)

III. HER2-CAR-NK for glioblastoma and breast cancer

Early data suggest these products are safe, scalable, and capable of inducing meaningful clinical responses.[7,8]

As NK-cell therapies advance into solid tumor settings, a clear understanding of NK-cell metabolism and exhaustion has become increasingly important. NK cells depend on tightly regulated metabolic pathways to sustain cytotoxicity, cytokine production, and proliferation, yet tumors exploit these metabolic requirements to suppress NK-cell function. Within the tumor microenvironment, hypoxia, nutrient competition, lactate accumulation, adenosine signaling, and TGF-β collectively impair NK-cell activation and drive functional exhaustion. Exhausted NK cells display reduced activating receptors, increased inhibitory checkpoints, diminished cytokine production, and weakened granule-mediated killing—features that arise from chronic stimulation typical of cancer.

To counter these pressures, next-generation NK-cell engineering strategies aim to enhance metabolic resilience and restore effector function. Cytokine-engineered NK cells expressing IL-15 or membrane-bound IL-21 show improved persistence and mitochondrial fitness.

Checkpoint blockade targeting NKG2A, T-cell immunoreceptor with Ig and ITIM domains (TIGIT), or programmed cell death protein-1 (PD-1) can reinvigorate NK-cell cytotoxicity, while metabolic reprogramming-such as enhancing glycolytic capacity or disrupting A2A receptor signaling-helps NK cells function in nutrient-poor, adenosine-rich environments. Additional innovations include CAR designs that incorporate chemokine receptors to improve tumor trafficking or hypoxia-responsive elements that activate selectively within low-oxygen niches. Combination approaches, such as pairing NK cells with monoclonal antibodies or oncolytic viruses, further amplify antitumor activity. Together, these strategies aim not only to help NK cells withstand the hostile tumor microenvironment but also to enable them to actively reshape it.

Conclusion

NK-cell–based immunotherapy has transitioned from a theoretical concept to a clinically validated therapeutic platform. Their innate safety, versatility, and compatibility with allogeneic manufacturing make NK cells uniquely suited for off-the-shelf cancer therapies. As our understanding of NK-cell metabolism, exhaustion, and TME interactions deepens, the next-generation engineered NK cells are poised to overcome the barriers that have historically limited immunotherapy in solid tumors. With multiple clinical trials demonstrating safety and promising efficacy, NK cells are emerging as a central pillar of the future immunotherapy landscape.

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Conflicts of interest

The author declares that there is no conflict of interests.

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