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Harnessing the Innate Effector: A Narrative Review of Advancing Strategies in CAR Engineering, Metabolic Reprogramming, and TME Resistance of Natural Killer Cells for Cancer Immunotherapy

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ABSTRACT

Natural Killer (NK) cell-based immunotherapy is rapidly emerging as a promising modality for cancer treatment. As pivotal players in the innate immune system, cells independently recognize and eliminate malignant cells without prior sensitization, offering distinct advantages over other cell-based therapies. This review highlights the current landscapes of NK cell adoptive therapy, from fundamental biology to cutting-edge clinical applications. It highlights how advancing NK cell sources, including peripheral blood, umbilical cord blood, established cell lines, and the increasingly significant induced pluripotent stem cells (iPSCs), are driving wider, more standardized therapeutic use. The multifaceted strategies employed to enhance NK cell efficacy are being explored, including advanced expansion protocols and sophisticated genetic engineering techniques such as the introduction of Chimeric Antigen Receptors (CARs) and modifications to bolster antibody-dependent cellular cytotoxicity. Additionally, it also addresses the significant hurdles that remain, primarily the immunosuppressive tumor microenvironment (TME), and discusses innovative strategies being developed to overcome these challenges. By synthesizing preclinical data and results from the latest clinical trials, this review highlights the remarkable progress and bright future of NK cell therapy as a safer, effective, and more accessible cornerstone of cancer treatment.

Keywords: Natural Killer (NK) cells; Cancer immunotherapy; CAR-NK cells; Induced pluripotent stem cells (iPSCs); Tumor microenvironment (TME); Adoptive cell therapy

1. INTRODUCTION

1.1. *The Innate Power of Natural Killer Cells*

For decades, cancer immunotherapy has focused on the adaptive immune system, especially T cells. The success of Chimeric Antigen Receptor (CAR)-T cell therapy in treating hematological malignancies has been revolutionary[1]. However, this success remains hampered by challenges, including life-threatening toxicities like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), the risk of graft-versus-host disease (GvHD) with allogeneic products, and the high cost and complexity of autologous manufacturing[2,3]

Natural Killer (NK) cells have garnered significant interest as a compelling alternative to T-cell-based immunotherapies. As a critical component of the innate immune system, NK cells constitute 5-15% of circulating lymphocytes and serve as the first line of defense against malignant and virally infected cells[4–6]. A dynamic balance of signals governs their anti-tumor function from activating and inhibitory receptors on their surface. Inhibitory receptors, such as Killer-cell Immunoglobulin-like Receptors (KIRs) and the Natural Killer group 2. Member A (NKG2A/CD94) complex, prevent autoimmunity by recognizing Major Histocompatibility Complex class I (MHC-I) molecules on healthy cells, while activating receptors, such as Natural Cytotoxicity Receptors (NCRs, like NKp30, NKp44, NKp46) and the Natural Killer group 2, member D (NKG2D), trigger cytotoxicity upon binding stress-induced ligands on tumors in an 'induced-self" mechanism[7]. Crucially, many cancer cells evade T-cells by downregulating MHC-I, a vulnerability that NK cells exploit through "missing-self" recognition, the removal of inhibitory signal licenses them for attack[4,8].

The cytotoxic responses of activated NK cells are mediated through several distinct pathways. The most direct is granule exocytosis, involving the targeted release of perforin and granzyme B into the immunological synapse to initiate target cell apoptosis[4,9]. A second pathway is death receptor-mediated cytotoxicity, facilitated by NK cell surface ligand such as Fas ligand (FasL) and THF-related apoptosis-inducing ligand (TRAIL) that engage death receptors on the susceptible tumor cells[10]. A third key mechanism is antibody-dependent cellular cytotoxicity (ADCC), in which the CD16 (FcγRIIIa) receptor binds to the Fc portion of antibodies opsonizing tumor cells, triggering the NK cell to destroy the target through the release of cytotoxic granules[8,11].

This potent effector functionality, combined with the MHC-independent nature of NK cells, allows for the safe use of allogeneic, or "off-the-shelf," products from healthy donors without the significant risks of GvHD, representing a major logistical and safety advantage over T-cell therapies[12,13]. Early clinical trials have validated the safety and feasibility of this approach, paving the way for a new generation of NK cell-based cancer treatments.

2. SOURCES OF NK CELLS FOR ADOPTIVE IMMUNOTHERAPY

A critical factor for successful NK cell therapy is obtaining a sufficient number of highly functional cells. Researchers have investigated several sources, each with a unique set of advantages and challenges.

2.1. Peripheral Blood (PB) and Umbilical Cord Blood (UCB)

Peripheral blood from healthy donors is the most accessible source of mature, cytotoxic NK cells. However, NK cells constitute only a small fraction of PBMCs (5-15%), necessitating significant *ex vivo* expansion to achieve therapeutic doses (10^5 to 10^8 cells/kg)[6,13]. While various expansion protocols exist, they can lead to cellular exhaustion, and the products often suffer from donor-to-donor variability and a short *in vivo* lifespan of about 7-10 days[14,15].

Umbilical cord blood offers a higher frequency of NK cells (around 30%) compared to peripheral blood and these cells demonstrate a greater proliferative capacity[16]. UCB-NK cells can be cryopreserved for long periods without significant loss of viability, making them an excellent source for creating banked, off-the-shelf therapies[17]. Functionally, UCB-NK cells respond robustly to

cytokine stimulation and can produce more IFN-γ than their PB counterparts, though they share the same challenge of donor variability[18].

2.2. NK Cell Lines

Cell lines such as NK-92, derived from a patient with non-Hodgkin's lymphoma, offer an unlimited, homogeneous, and easily manipulated source of NK cells[19]. The NK-92 cell line has been approved by the FDA for clinical trials and can be easily expanded to clinical grades. These cells express a range of activating receptors but lack the CD16 receptor, limiting their ADCC potential unless genetically engineered[20]. A significant safety consideration is their malignant origin, which necessitates irradiation before infusion, thereby limiting their *in vivo* persistence and proliferative capacity[21].

2.3. Induced Pluripotent Stem Cells (iPSCs)

The development of induced pluripotent stem cells (iPSCs) represents a paradigm shift for cellular therapy, including NK cell production[22]. iPSCs can be generated from somatic cells (like skin or blood cells) and possess two crucial properties: indefinite self-renewal and the ability to differentiate into any cell type, including NK cells[1]. This technology enables the creation of a clonal, master iPSC line that can be extensively characterized, genetically engineered, and then used as a renewable source for the mass production of homogeneous, therapeutic-grade NK cells (iNK cells)[13,23].

iPSC-derived NK (iNK) cells present significant advantages that address key limitations of other cell sources. Primarily, they offer an unlimited and standardized supply, overcoming donor dependency and product variability to facilitate genuine "off-the-shelf" application[13,23]. Moreover, the iPSC platform is uniquely suited for advanced genetic engineering[24]**;** modifications can be performed with high efficiency at the master cell line stage, ensuring that 100% of the resulting NK cell population carries the desired trait[25]. These attributes collectively enable the establishment of large, cryopreserved banks of therapeutic cells, ensuring a readily available and homogenous product for clinical use[25,26].

Despite immense promise, the clinical translation of iPSC-NK therapies has faced strategic hurdles. In 2023, Fate Therapeutics, a pioneer in the field, discontinued several of its leading iPSC-NK cell programs, including FT516 and FT596, citing a challenging financial environment and a strategic shift[13]. This highlights the significant costs and complexities associated with bringing these novel therapies to market, even with a robust scientific foundation. Nevertheless, the iPSC platform remains a vital area of research, with ongoing efforts to optimize manufacturing and demonstrate long-term clinical benefit.

3. ENGINEERING A MORE POTENT NK CELL

To maximize the therapeutic potential of NK cells, particularly against solid tumors, researchers are employing a variety of genetic engineering strategies to enhance their function, persistence, and tumor-homing capabilities.

3.1. Chimeric Antigen Receptors (CARs): Directing NK Cells to the Tumor

The transformative success of CAR-T cells has been adapted for NK cells. CARs are synthetic receptors that redirect immune cells to recognize specific tumor-associated antigens (TAAs) via a single-chain variable fragment (scFv) derived from an antibody[27]. While early CAR-NK studies utilized constructs designed for T cells (e.g., with CD28 and 4-1BB costimulatory domains), recent efforts focus on incorporating signaling domains native to NK cells to optimize their activation[28]. A pivotal study identified a CAR containing the NKG2D transmembrane domain, the 2B4 co-stimulatory domain, and the CD3ζ signaling domain as a highly effective construct for mediating antigen-specific NK cell signaling and potent anti-tumor activity[29]. This NK-specific CAR design (NK-CAR) demonstrated superior killing of ovarian cancer cells compared to a traditional T-cell-based CAR (T-CAR) when expressed in iPSC-NK cells, both *in vitro* and *in vivo*. The modularity of CAR design allows for the incorporation of various NK-derived domains such as DAP10, DAP12, and FcRy to further tune the cellular response[4].

Several CAR-NK cell therapies are in clinical trials for both hematological and solid tumors (Table 1). A landmark trial using cord blood-derived CD19-CAR-NK cells co-expressing IL-15 demonstrated an impressive 73% response rate in patients with B-cell malignancies, with no major toxicities observed[30]. Products like NKX019 (targeting CD19)[31] and NKX101 (an NKG2D-based CAR from Nkarta Therapeutics)[32] are also showing promising early results in B-cell malignancies and AML, respectively, with high rates of complete remission in some patient cohorts.

3.2. Enhancing Antibody-Dependent Cellular Cytotoxicity (ADCC)

A key innate function of NK cells is ADCC, mediated by the CD16a receptor. This can be therapeutically leveraged by combining NK cell infusions with tumor-targeting monoclonal antibodies. However, upon activation, CD16a is cleaved from the NK cell surface by the metalloproteinase ADAM17[11], limiting sustained ADCC. Engineering strategies to overcome this include introducing a high-affinity, non-cleavable variant of CD16a (hnCD16)[33,34]. iPSC-NK cells engineered with hnCD16 (e.g., FT516) exhibit enhanced and sustained ADCC in combination with antibodies like rituximab (anti-CD20), making this a powerful combination strategy.

3.3. Improving Persistence, Proliferation, and Trafficking

A major limitation of adoptive NK cell therapy is their short *in vivo* persistence. To overcome this, several innovative strategies are being developed, focusing on cytokine engineering, targeting inhibitory checkpoint disruption, metabolic fitness enhancement, and improved tumor homing[35]. A cornerstone approach involves harnessing Interleukin-15 (IL-15), a key cytokine for NK cell survival and proliferation that, unlike IL-2, does not significantly expand immunosuppressive regulatory T cells (Tregs)[36]. By engineering NK cells to constitutively express IL-15, either as a secreted or membrane-bound form (e.g., an IL-15/IL-15Rα fusion construct), creates an autocrine loop that promotes their autonomous growth and persistence[36]. This strategy has been successfully incorporated into several CAR-NK clinical candidates.

Beyond providing growth signals, enhancing the NK cell's intrinsic response to them is equally critical. The gene *CISH*, encoding the protein CISH (cytokine-inducible SH2-containing protein), is a negative regulator of IL-15 signaling[37]. Knocking out *CISH* in iPSC-NK cells has been shown to enhance their metabolic fitness, increase their sensitivity to IL-15, and promote superior *in vivo* persistence and anti-tumor activity[37]. Similarly, targeting the metabolic pathway directly has

shown promise. A feature of long-lived "adaptive" NK cells is the downregulation of CD38, an ectoenzyme that consumes NAD+. Engineering iPSC-NK cells with a CD38 knockout has been shown to elevate intracellular NAD+ levels, leading to enhanced metabolic fitness and resistance to oxidative stress, thereby improving persistence and function[38]. Finally, to ensure NK cells can effectively reach their target, strategies are being employed to overcome the poor infiltration into solid tumors. This is achieved by engineering NK cells to express specific chemokine receptors, such as CXCR1 or CXCR2[39,40], that match the chemokine profile secreted by the tumor. This acts as a molecular "GPS," guiding the NK cells directly to the tumor site.

4. OVERCOMING THE HURDLES: THE TUMOR MICROENVIRONMENT AND BEYOND

Despite these promising advances, the efficacy of NK cell therapy, especially in solid tumors, is significantly hampered by the hostile tumor microenvironment (TME).

4.1. Mechanisms of TME-Mediated Suppression

The tumor microenvironment (TME) suppresses Natural Killer (NK) cell function through a multi-faceted assault. Physically, a dense extracellular matrix (ECM) acts as a barrier to infiltration[41]. Once in the TME, NK cells face a hostile milieu of soluble immunosuppressants like Transforming Growth Factor-β (TGF-β), which directly inhibit NK cell proliferation, metabolism, and cytotoxicity by downregulating key activating receptors like NKG2D[42]. Furthermore, the TME is metabolically antagonistic, as hypoxia, nutrient deprivation, and accumulated waste products like lactate starve NK cells of energy[43]. Finally, the engagement of inhibitory checkpoints, such as PD-1 on NK cells with PD-L1 on tumor cells, induces functional exhaustion, effectively shutting down the anti-tumor immune response[44].

4.2. Strategies to Overcome TME Resistance

To counter the suppressive tactics of the tumor microenvironment (TME), several advanced engineering and combination strategies are being deployed. A primary focus is on directly engineering resistance to soluble inhibitors like TGF-β; this is achieved by equipping NK cells with dominant-negative TGF-β receptor (DNTGFβRII). This modification acts as a shield, preventing the inhibitory signal and preserving the NK cells' cytotoxic function within the TME[45]. Another innovative approach converts the inhibitory signal into an activating one by fusing the TGF-β receptor's external domain to an activating intracellular domain like NKG2D or DAP12[36]. Furthermore, the combination of adoptive NK cell therapy with immune checkpoint inhibitors (ICIs) can effectively reinvigorate exhausted NK cells, demonstrating synergistic clinical benefits for cancers like NSCLC[46].

Another powerful approach involves the use of NK cell engagers, bispecific or trispecific killer engagers (BiKEs and TriKEs) are novel antibody constructs that act as a bridge, simultaneously binding to an activating receptor on NK cells (like CD16 or NKp46) and a tumor-associated antigen[13]. This forces a close proximity and potent activation of the NK cell against the tumor target. Some TriKEs also include an IL-15 moiety to further stimulate NK cell activity and proliferation[47]. The efficacy of this strategy is highlighted by the remarkable 97% overall response rate observed in a trial combining the CD30-targeting engager AFM13 with cord blood NK cells for refractory lymphoma[48]

Quantitative analysis revealed slight variations in the percentage of positive cells among the passages. The expression of CD105 and CD73 remained relatively stable from passage 6 through passage 9, showing no statistically significant differences. In contrast, a reduction in CD90 expression was observed at later passages. Specifically, CD90-positive cells decreased from high levels at early passages to 67.3% and 64.3% at passages 8 and 9, respectively (Figure 2 and 3). Despite this decline, all cell populations continued to meet MSC immunophenotypic criteria, suggesting that extended in vitro expansion did not compromise the overall mesenchymal identity of UC-MSCs, though it may influence specific surface marker expression associated with stemness.

5. THE CLINICAL LANDSCAPE AND FUTURE PROSPECTS

Natural Killer (NK) cell therapy is rapidly advancing from a promising concept to a tangible clinical modality, with a diverse pipeline from unmodified allogeneic NK cells to highly engineered iPSC-derived CAR-NK products. While early trials showed modest but encouraging results, particularly in hematological malignancies, the new generation of engineered NK cells is demonstrating significantly improved response rates with an excellent safety profile.

The future of NK cell immunotherapy is poised for transformative growth, guided by several key trajectories. First, the rise of "off-the-shelf" platforms, especially those utilizing iPSC-derived NK cells are set to become a cornerstone of cancer therapy, offering a scalable, consistent, and cost-effective solution that can be made readily available to patients6. Second, to overcome tumor heterogeneity and antigen escape, next-generation products are incorporating multi-antigen targeting and sophisticated logic-gated systems, enhancing both tumor specificity and safety4. Third, the full potential of NK cells will likely be unlocked through synergistic combination therapies, partnering them with NK cell engagers, monoclonal antibodies, and even conventional therapies like radiotherapy, which can make tumors more susceptible to NK cell attack4. Finally, the implementation of intelligent, automated, closed-system manufacturing platforms, potentially guided by artificial intelligence, will be crucial to standardize production, reduce costs, and ensure the high quality of NK cell products for widespread clinical use6. Together, these advancements are charting a course for NK cells to become a mainstay in the next generation of cancer treatment.

CONCLUSION

In conclusion, NK cell-based immunotherapy has transitioned from a promising concept to a clinical reality with the potential to reshape cancer treatment. Their inherent safety, potent anti-tumor activity, and amenability to advanced genetic engineering, particularly through the iPSC platform, position them as a vital tool in the next generation of cancer immunotherapies. As research continues to unravel the complexities of NK cell biology and overcome existing challenges, we can anticipate a future where these "natural killers" play a central role in providing effective and accessible therapies for a broad range of cancers

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Competing Interests

The authors declare that there is no conflict of interest.

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