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REVIEW

Bringing natural killer cells to the clinic: Opportunities beyond cancer

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Natural killer (NK) cells are cytotoxic and cytokine-producing innate lymphocytes with established roles in antiviral and antitumor immunity. In recent years, the biology of NK cells has been exploited in innovative cancer immunotherapies, leading to clinical advances including allogeneic NK cell infusions, chimeric antigen receptor NK cells, and NK cell engager technologies. These studies pave the way to explore how advances in NK cell–based immunotherapies could be leveraged outside of oncology to selectively target pathogenic cells and restore tissue homeostasis in viral infections, neurodegenerative disorders, autoimmunity, and transplantation medicine.

Introduction

Natural killer (NK) cells are lymphocytes belonging to the innate lymphoid cell (ILC) family (Vivier et al., 2018). Together with ILC1, they constitute group 1 ILCs and have been recognized for their ability to eliminate virally infected and malignant cells without prior antigen-specific sensitization. Through a combination of activating and inhibitory receptors, NK cells can distinguish healthy self from altered self. Indeed, NK cells can detect self-molecules that appear or increase on stressed cell surfaces. A classic illustration of this stress-related self-detection involves NK cell activation through activating surface receptors like NKG2D and the natural cytotoxicity receptors (NCRs), NKp46 and NKp30. These receptors bind to Major histocompatibility complex (MHC) class I chain-related protein A and B (MICA/B) and UL16-binding proteins (ULBPs), ecto-calreticulin, or B7-H6, respectively, which are displayed on stressed cells. The expression of these ligands occurs following DNA damage responses, excessive cell proliferation, or other stress-triggered signaling cascades. NK cells also express inhibitory surface receptors such as killer cell immunoglobulin-like receptors (KIRs) that recognize major histocompatibility complex (MHC) class I molecules and CD94/NKG2A that recognizes the nonclassical MHC class I molecule, HLA-E (Vivier et al., 2024). Once activated, NK cells ensure a rapid immune response by killing distressed cells and releasing an array of chemokines and cytokines that shape a broader immune response. Advances in understanding NK cell biology have spurred innovative therapies that leverage their unique functional capacities (Laskowski et al., 2022; Myers and Miller, 2021; Vivier et al., 2024).

Candidate therapeutic strategies aimed at harnessing NK cells for cancer treatment comprise monoclonal antibody–based therapies, such as bispecific or multispecific NK cell engagers and immune checkpoint inhibitors (targeting NKG2A, LAG-3, TIGIT, or TIM-3), or cell-based therapies infused directly into patients such as ex vivo–expanded or genetically modified NK cells including CAR-NK cells (Laskowski et al., 2022; Myers and Miller, 2021; Vivier et al., 2024). NK-based therapies exhibit a favorable safety profile; notably, NK cells do not trigger graft-versus-host disease. Their potential for "off-the-shelf" manufacturing from allogeneic sources is an attractive feature to increase scalability and cost-effective manufacturing. Clinical trials based on NK cell–based therapies are in phase I and I/II stages, and are targeting a broad spectrum of cancers, including various lymphomas, leukemias, and solid tumors (Biederstädt and Rezvani, 2025; Laskowski et al., 2022; Myers and Miller, 2021; Vivier et al., 2024). However, there are still some challenges, particularly with regard to the persistence and fitness of NK cells *in vivo* in the immunosuppressive tumor microenvironment, as well as the manufacturing and scalability of the therapies (Shi et al., 2024). Despite these hurdles, the field is exploring new strategies such as metabolic engineering, next-generation "armored" NK cells with improved homing and survival capabilities, and computational tools to refine target identification and predict therapeutic responses (Burga et al., 2019; Du et al., 2021; Foo et al., 2023).

While NK cell–based therapies are emerging, the most transformative immunotherapy successes to date have come from the harnessing of T cell immunity. The use of immune

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checkpoint inhibitors, bispecific antibodies, and CAR-T cells has led to major clinical advances in cancer. Recently, T cell–based immunotherapies have been pivoted to other disease conditions. In particular, CAR-T cells targeting B cell surface molecules have been used in patients presenting B cell–mediated autoimmunity with groundbreaking clinical benefit. Similarly, although NK cell therapies currently focus on cancer, their functional repertoire and excellent safety record suggest broader therapeutic potential. Indeed, NK cells are more than killers of tumor cells. Their effector functions can be redirected against normal cells in an autologous setting with stimulating engagers binding to defined target surface molecules. In addition, accumulating evidence reveals that NK cells can be present in nearly all tissues (Björkström et al., 2016; Dogra et al., 2020). Together, these findings support the investigation of NK cell therapies beyond cancer. We review current insights into human NK cell heterogeneity and function, their roles in viral infection, autoimmunity, neurodegeneration, and transplantation, and the emerging therapeutic opportunities they offer.

What are NK cells?

Over the five decades since their discovery, major advances have been made in deciphering the heterogeneity of NK cells (Kiessling et al., 1975). In human, NK cells were initially classified into two main subsets based on the surface expression of CD56, encoded by the neural cell adhesion molecule 1 *NCAM1* gene, and the Fcγ receptor III (CD16), encoded by *FCGR3A* (Cooper et al., 2001; Lanier et al., 1983; Lanier et al., 1986). These subsets commonly referred to as $CD56^{dim}$ and $CD56^{bright}$ NK cells (Moretta, 2010; Vivier et al., 2008) differ not only in phenotype but also in function and tissue localization. $CD56^{dim}$ cells exhibit strong cytotoxic potential and highly express perforin, granzymes, and CD16, endowing them with an antibody-dependent cellular cytotoxicity (ADCC) capacity. They also express KIRs and chemokine receptors such as CX3CR1 and CXCR1, which enable peripheral tissue recruitment. $CD56^{dim}$ cells also produce an array of proinflammatory cytokines (IFN-γ, TNF-α), chemokines (CCL3/4/5), and immunomodulatory molecules (TGF-β, IL-10). By comparison, $CD56^{bright}$ NK cells are professionalized in soluble factor production (Horwitz et al., 1999; Vivier and Ugolini, 2009). They express little or no CD16 or KIRs, but are enriched in CCR7 and CD62L (L-selectin), which supports homing to secondary lymphoid tissues (Collins et al., 2019; Cooper et al., 2001; Freud et al., 2017; Jacobs et al., 2001). $CD56^{dim}$ are the predominant population in peripheral blood and highly vascularized tissues, including bone marrow, spleen, lung, and breast. $CD56^{bright}$ are preferentially enriched in lymph nodes, tonsils, liver, uterus, and throughout the gastrointestinal tract (Dogra et al., 2020; Ferlazzo and Carrega, 2012; Melsen et al., 2016; Sender et al., 2023; Subedi et al., 2022; Vivier et al., 2024; Yu et al., 2013). However, accumulating evidence has revealed that NK cells span a broader and more nuanced continuum, thereby challenging the traditional dichotomy (Freud et al., 2017). For instance, a third subset of $CD56^{neg}$ NK cells has been described. These cells are rare in healthy individuals and proliferate in certain pathological conditions such as chronic and acute viral infections (e.g., human immunodeficiency virus, hepatitis C virus) and acute myeloid leukemia, but their function remains debated (Björkström et al., 2010b; Gonzalez et al., 2009; Gyurova et al., 2019; Stary et al., 2020; Wlosik et al., 2025).

Furthermore, terminally differentiated "adaptive" NK cells exhibiting memory-like features, originally described in mouse models of cytomegalovirus (CMV) infection (Sun et al., 2009), are now also characterized in humans (Hammer and Romagnani, 2017; Lopez-Vergès et al., 2010). They show selective target recognition of human cytomegalovirus (HCMV)-infected cells via the CD94-NKG2C receptor complex and enhanced functionality. Paralleling memory T cell differentiation, adaptive NK cells acquire epigenetically imprinted transcriptional programs that promote long-term persistence and antigen-specific recall responses (Lee et al., 2015; Rückert et al., 2022; Tesi et al., 2016). Memory-like NK cell responses are not restricted to HCMV exposure, as subsets with similar properties have also been observed following infection with hantavirus (Björkström et al., 2010a), human immunodeficiency virus (Vendrame et al., 2020), influenza virus (Jost et al., 2023), and SARS-CoV-2 (Hasan et al., 2024), suggesting a broader paradigm (Lopez-Vergès et al., 2011). In addition, cytokine-induced memory-like (CIML) NK cells can be generated independently of virus recognition, following stimulation with a cocktail of IL-12, IL-15, and IL-18 (Cooper et al., 2009; Cooper and Yokoyama, 2010; Romee et al., 2012). CIML cells persist long term and show an enhanced response to further restimulation that partially recapitulates properties associated with adaptive NK cells (Hammer and Romagnani, 2017; Terrén et al., 2022).

Over the past decade, advances in single-cell "omics" technologies, such as single-cell RNA sequencing, have transformed our ability to study immune cell diversity and substantially refined our understanding of NK cell heterogeneity (Subedi et al., 2022). In particular, three major subsets in healthy blood—NK1, NK2, and NK3—have been identified (Rebuffet et al., 2024; Vivier et al., 2024). NK1 corresponds to $CD56^{dim}CD16^{+}$ NK cells, NK2 to $CD56^{bright}CD16^{-}$ and early-stage $CD56^{dim}$, while NK3 includes, but is not limited to, $CD16^{dim}$ $NKG2C^{+}CD57^{+}$ adaptive NK cells. The subpopulations within the NK1 and NK2 clusters—namely, NK1A, NK1B, NK1C, and NKint—recapitulate subsets identified in previous single-cell transcriptomics analyses (Crinier et al., 2018; Jaeger et al., 2024; Melsen et al., 2016; Smith et al., 2020; Yang et al., 2019). An alternative strategy has been obtained based on the label transfer of transcriptional signatures derived from sorted populations based on CD56, NKG2A, KIR, CD57, and NKG2C cell surface expression (Björkström et al., 2010c; Netskar et al., 2024). There is some overlap with the NK1-3 framework (Rebuffet et al., 2024), but a key distinction lies in the presumed fate of $CD56^{bright}$ cells. Indeed, the $CD56^{dim}$ and $CD56^{bright}$ subsets have been interpreted through a maturation lens (Holmes et al., 2021; Netskar et al., 2024; Subedi et al., 2022), with $CD56^{bright}$ NK cells possibly representing the most immature or naïve state (Chan et al., 2007; Dulphy et al., 2008), while $CD56^{dim}$ NK cells comprising more differentiated stages, which has been associated with a gradual downregulation or upregulation of surface molecules such as CD62L (*SELL*), NKG2A (*KLRC1*), or CD57, KIRs, and NKG2C (*KLRC2*), respectively

(Björkström et al., 2010c; Juelke et al., 2010). This trajectory of NK cell differentiation from CD56^{bright}KIR^{-} to CD56^{dim}KIR^{+} cells is challenged by the absence of experimental data showing such a transition. In addition, data in human and mouse support two development routes for NK cells: one from early NK cell progenitors giving rise to NK1 and NK3, and the other from the innate lymphoid common progenitor leading to NK2 (Ding et al., 2024).

Another layer of heterogeneity arises from the tissue in which NK cells reside, with the local microenvironment exerting a strong imprint on differentiation (Björkström et al., 2016), transcriptomics profile (Crinier et al., 2018), and functional properties (Subedi et al., 2022). Tissue-resident NK cells express residency markers such as CD69 and CXCR6 in the liver (Aw Yeang et al., 2017; Cuff et al., 2016; Hudspeth et al., 2016; Stegmann et al., 2016) and lymphoid tissues (Crinier et al., 2021a; Lugthart et al., 2016), CD49a and CD103 in the uterus, tonsil, and lung, and various chemokine receptors (Carrega et al., 2014; Maghazachi, 2010) that limit their egress into the circulation (Björkström et al., 2016; Melsen et al., 2016; Subedi et al., 2022). An analysis identified *RGS1* (regulator of G protein signaling 1) as a transcriptional marker for tissue-infiltrating NK cells (Tang et al., 2023). In several tissues, they have been shown to have functional differences from their blood counterparts (Dogra et al., 2020; Marquardt et al., 2017; Robinson et al., 1984), the most prominent example being uterine NK cells, which have been proposed to play a role in placental vascular remodeling and regulation of trophoblast invasion (Gaynor and Colucci, 2017).

Similarly, NK cells are significantly altered by the tumor microenvironment (de Andrade et al., 2019; Li et al., 2025; Liang et al., 2022; Pietropaolo et al., 2021; Zu et al., 2024), conditions in which a terminal stage CD56^{dim} population was identified and therefore termed tumor-associated NK cells. These cells are poorly cytotoxic, display a stressed phenotype, and are potentially dysfunctional. This subset is associated with poor survival and immunotherapy resistance in various cancers.

Finally, the last piece of the puzzle lies in the close ontological and functional proximity between NK cells and ILC1. Increasing evidence highlights a high degree of plasticity between those two populations, which can have overlapping phenotypes, localizations, and functions to some extent (Björklund et al., 2016; Chaudhry and Belz, 2024; Jaeger et al., 2024; Spits et al., 2016). Importantly, cytotoxicity, once considered a defining feature of NK cells, can also be attributed to subsets of ILC1, further blurring their distinction. The NK-ILC1 convergence has been described in the tumor microenvironment, where transforming growth factor β (TGF-β) in particular has been shown to reprogram NK cells into resident ILC1-like cells with impaired antitumor capacity (Cortez et al., 2017; Crinier et al., 2021b; Picant et al., 2025).

Regardless of these different characteristics of NK cells, the standardized NK1, NK2, and NK3 terminology aims to promote clarity and consistency in future research, thereby improving the comparability of studies. This last point is crucial, considering that CD56 is not expressed in mouse NK cells, while NK1 and NK2 have been identified in both humans and mice (Crinier et al., 2018; Lopes et al., 2022). Despite the limitations of the CD56^{dim} and CD56^{bright} NK cell classification and the improvement offered by the NK1, NK2, and NK3 terminology, published studies on NK cell subsets that employed the CD56^{dim} and CD56^{bright} nomenclature will be presented herein using their original terminology.

NK cells in viral infections

NK cells recognize virus-induced molecules on infected cell surfaces, triggering direct cytotoxicity and secretion of cytokines (IFN-γ, TNF-α) that control viral replication. Paradoxically, long-term follow-up of patients with selective ILC deficiency revealed no increased susceptibility to common viral infections (Vély et al., 2016), suggesting that under conditions of modern hygiene and medical care, NK cell functions against most viruses may be redundant or compensated by other immune mechanisms. However, studies of primary immunodeficiencies affecting—though not restricted to—NK cells (Abdalgani et al., 2025; Mace and Orange, 2019) support a role of NK cells in controlling flaviviruses (Blom et al., 2016; Marquardt et al., 2015; Zimmer et al., 2019) and herpesviruses. Among herpesviruses, CMV represents the best-characterized example of NK cell–mediated immune control.

NK cells may serve as essential effectors against specific viruses in contexts where other immune compartments are compromised. During pregnancy, for instance, the maternal–fetal interface develops as an immunosuppressive environment that maintains T cell tolerance toward the fetus. In this setting, intrauterine immune surveillance—notably against CMV—appears to be mediated by decidual NK cells (Pighi et al., 2024; Siewiera et al., 2013; Yockey and Iwasaki, 2018). Similarly, increased CMV susceptibility has been observed in patients experiencing delayed NK cell reconstitution following hematopoietic stem cell transplantation (HSCT) (Cook et al., 2006; Park et al., 2020). Furthermore, in pediatric patients with immature immune systems, complete NK cell functional impairment (though the selectivity of this deficiency remains unclear) has been associated with heightened susceptibility to Epstein-Barr virus (EBV) (Fleisher et al., 1982).

Beyond their physiological role in antiviral immunity, therapeutic strategies exploiting NK cell antiviral properties are being explored for chronic viral infections with potential for severe disease progression. In a clinical study of 16 patients, early adoptive NK cell infusion following HSCT protected against human herpesvirus-6B reactivation (Gasior et al., 2021). In HIV-infected patients, observations of NK cells dysfunction have prompted two phase I clinical trials evaluating combined NK cell infusion with IL-2 or IL-15 superagonists to enhance NK cell fitness (NCT03346499 and NCT03899480 [Miller et al., 2024], respectively). These trials reported favorable safety profiles and modest reductions in HIV RNA-positive cells. Despite the success of SARS-CoV-2 vaccines, several clinical trials have evaluated whether NK cell–based therapies could improve disease outcomes. A phase I/II trial (NCT04578210) demonstrated that infusion of allogeneic NK cells from convalescent donors into patients with moderate-to-severe COVID-19 was safe and

well tolerated (Hernández-Blanco et al., 2025). Similarly, ongoing phase I trials are assessing the safety of genetically modified placental-derived NK cells (NCT04365101), iPSC-derived NK cells expressing noncleavable CD16 (NCT04363346), and cord blood–derived allogeneic NK cells—either unmodified (NCT04900454) (Liu et al., 2024) or as CAR-NK cells overexpressing NKG2D, the SARS-CoV-2 receptor ACE2, an IL-15 superagonist, and a GM-CSF–neutralizing antibody (NCT04324996). Most trials remain ongoing and are at early stages. Completed phase I studies collectively demonstrate the safety of NK cell–based therapies for viral infections; however, additional studies are required to establish their therapeutic efficacy (Fig. 1). Leveraging NK cell immunity to target infected cells through specific antigen recognition may represent a promising complementary strategy for future therapeutic development.

NK cells in neurodegenerative diseases

The traditional view of the central nervous system (CNS) as an "immune-privileged" ecosystem, firmly independent and sealed from peripheral immune cells, has drastically evolved. This shift stems from the discovery of neuroimmune interfaces that permit afferent cell trafficking and immune surveillance, including by NK cells, which are necessary for CNS homeostasis (Castellani et al., 2023; Rustenhoven et al., 2021). Despite their clinical diversity, many neurodegenerative diseases share pathological hallmarks, suggesting a convergence of the underlying processes. It is possible to distinguish neurodegenerative disorders relying on genetic mutations and intraneuronal mechanisms (Kamatham et al., 2024; Wilson et al., 2023) from diseases in which pathogenesis is driven by extracellular elements. These include misfolded protein aggregates, autoreactive T cells (Campisi et al., 2022; Huseby et al., 2001; Lalle et al., 2024; Lückel et al., 2019; Machado-Santos et al., 2018; Monsonego et al., 2003), or chronically activated microglial cells (Melchiorri et al., 2023; Webers et al., 2020), which cumulatively disrupt brain barriers and create a persistent neurotoxic inflammatory environment (Sweeney et al., 2018).

There are several lines of evidence for the presence of a small population of tissue-resident NK cells in the CNS of healthy individuals. In humans, although studies are limited due to inaccessibility of the tissue, NK cells, mostly with a CD56^{bright} (NK2) phenotype, have been detected in both the cerebrospinal fluid and brain parenchyma (Gross et al., 2016; Qin et al., 2024). *In vitro* experiments using human brain microvascular endothelial cells demonstrated a higher adherence and transmigration capacity of CD56^{bright} cells (Gross et al., 2016). In mice, NK cells have consistently been observed in limited numbers within the brain parenchyma (Korin et al., 2017; Mrdjen et al., 2018) and in proximal immune cell niches (i.e., subdural meninges, dura mater, and choroid plexus) (Van Hove et al., 2019). These findings collectively indicate that NK cell passage across the CNS barriers is rare under homeostatic conditions. Yet, peripheral NK cells have been shown to infiltrate CNS in various inflammatory contexts (Lepennetier et al., 2019) and increasing number of studies implicate NK cells in the pathophysiology of inflammatory-driven neurodegenerative diseases (Fig. 1 and Table 1).

In multiple sclerosis (MS), a chronic autoimmune disease (AID) of the CNS (Jilek et al., 2007; Rodríguez Murúa et al., 2022), NK cells, mainly of the CD56^{bright} phenotype, are found in increased frequencies both in the cerebrospinal fluid (Gross et al., 2016; Rodríguez-Martín et al., 2015; Schafflick et al., 2020) and in the brain parenchyma of patients (Liu et al., 2016; Rodríguez-Lorenzo et al., 2022), with an accumulation observed in active lesions and in close proximity to T cells. Mechanistically, NK cell recruitment is mediated by CXCL9, CXCL10, and CCL2 secreted by astrocytes and microglia, as well as neuron-derived CX3CL1 (Huang et al., 2006). Once in the CNS parenchyma, neuron stem cell IL-15 secretions sustain NK cell survival, proliferation, and fitness (Liu et al., 2016). In MS animal models, NK cell depletion exacerbates disease severity, while adoptive transfer alleviates symptoms (Hao et al., 2010; Zhang et al., 1997). These protective effects are mediated through both the secretion of immunosuppressive factors (i.e., acetylcholine and cytokines) (Jiang et al., 2017; Sanmarco et al., 2021) and direct cytotoxicity against autoreactive T cells (Jiang et al., 2011). Consistently, expansion of intrathecal CD56^{bright} in MS patients treated with a CD25 blocking antibody (daclizumab) correlated with therapeutic outcomes (Bielekova et al., 2006; Bielekova et al., 2011; Martin et al., 2010; Wynn et al., 2010), whereas active phases or relapses are frequently associated with altered NK cell number, phenotype, and cytolytic activity against autoreactive CD4^{+} T cells (Caruana et al., 2017; Gross et al., 2016; Laroni et al., 2016). Although few studies report a detrimental role of NKp46^{+}/NK1.1^{+} ILCs in disease recovery in mouse models (Kwong et al., 2017; Liu et al., 2016), notably by promoting brain barrier permeabilization and T cell entry into the CNS, NK cells are generally associated with treatment efficacy and clinical remission. Another study links poor NK cell function to ineffective control of EBV-induced autoimmunity, leading to an increased risk of MS (Vietzen et al., 2023). In individuals with high antibody titers to EBNA386–405, which cross-reacts with the glial protein GlialCAM, autoreactive T and B cells may emerge but are normally eliminated by NK cells. Two subsets are particularly important: NKG2C^{+} adaptive NK cells, primed by prior HCMV infection, and NKG2D^{+} NK cells, which recognize stressed lymphocytes. The protective effect requires specific host and viral traits, such as HCMV strains that stabilize HLA-E and highly active NKG2D genotypes, which are common in healthy EBNA^{high} individuals but rare in MS patients. In MS, autoreactive B cells evade NK killing by upregulating HLA-E through EBV-driven mechanisms, engaging inhibitory NKG2A receptors, and blocking cytotoxicity. Overall, NK cells emerge as sentinels eliminating autoreactive clones induced by viral mimicry, with outcomes determined by the balance of activating (NKG2C, NKG2D) and inhibitory (NKG2A–HLA-E) signals. Genetic variation, prior viral exposures, and viral strain diversity modulate this balance, highlighting therapeutic opportunities in boosting protective NK subsets, enhancing activating pathways, or blocking inhibitory checkpoints to restore tolerance in EBV-associated autoimmunity.

Alzheimer's disease (AD) is a multifactorial disorder traditionally characterized by the accumulation of extracellular Aβ

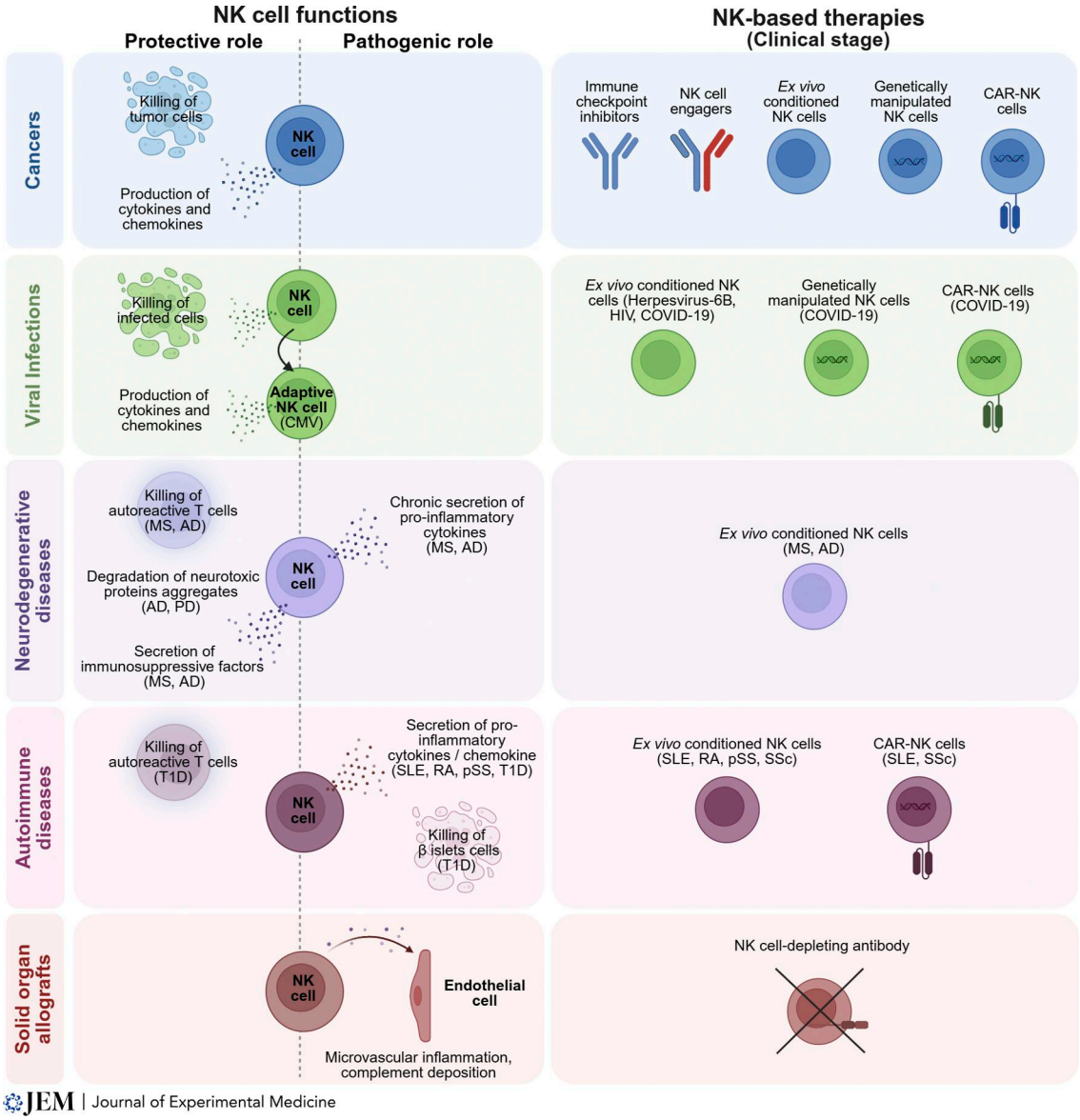

Figure 1. **Endogenous role and harnessing possibilities of NK cells in cancer and beyond.** NK cells are well recognized for their capacity to detect and eliminate tumor cells. Several strategies to harness these functions have been developed and are currently being evaluated in clinical trials for both hematologic malignancies and solid tumors. These advances are now being extended to investigate the potential of NK cell manipulation in other clinical contexts, including viral infections, neurodegenerative disorders, AIDs, and solid organ transplantation.

aggregates and neuroinflammation (Leng and Edison, 2021). However, recent evidence revealed a significant contribution from intrathecal chronically activated T cells, establishing autoimmune responses as a hallmark of AD pathology (Afsar et al., 2023; Gate et al., 2020). While not all patients diagnosed with mild cognitive impairment (MCI) will progress to AD, they are at increased risk, suggesting that MCI may represent an early stage of the disease (Bradfield, 2023; Levey et al., 2006). Although there are no studies comparing the CNS NK cells of MCI and AD patients with age-matched healthy individuals, most available data indicate that the number of circulating NK cells remains unchanged in these groups (Huang et al., 2022; Le Page et al., 2015; Richartz-Salzburger et al., 2007). In contrast, NK cell frequencies have been shown to increase specifically in the cerebrospinal fluid of MCI and AD patients (Busse et al., 2021), possibly due to an increase in CX3CL1 (Kulczyńska-Przybik et al., 2020). Their precise functional state and role are still unknown: a proinflammatory phenotype has been observed specifically in CSF NK during the MCI stages (Le Page et al., 2015), while *ex vivo* assays of blood NK cells reported variable alterations in their fitness, ranging from increased to impaired cytotoxic functions (Araga et al., 1991; Le Page et al., 2015; Solerte et al., 1998). Both human studies and animal models support a protective role of NK cells through their ability to clear Aβ aggregates, either by direct uptake and degradation (Zúñiga et al., 2025) or by reinvigorating the phagocytic capacity of microglia (Hwang et al., 2022). As described in MS, NK cells may also reduce neuroinflammation and glial proinflammatory phenotype

Table 1. **NK cell characteristics in neurodegenerative diseases**

Disease	Circulating NK cells	CSF NK cells	CNS parenchyma NK cells	Predominant phenotype	Activation/ functional status	Protective mechanisms	Detrimental effects
MS	Altered number	↑	↑ Accumulate in active lesions near T cells	CD56^{bright}	Variable cytolytic activity during relapses	Kills autoreactive CD4$^+$ T cells; secretes acetylcholine and immunosuppressive cytokines; NKG2C$^+$ and NKG2D$^+$ subsets eliminate EBV-induced autoreactive clones	NKp46$^+$/NK1.1$^+$ ILCs promote brain barrier permeabilization and T cell CNS entry; autoreactive B cells evade killing via HLA-E upregulation
AD	Unchanged	↑	Not well defined	CD56^{bright} (predominant in CNS)	Proinflammatory in CSF during MCI; variable blood; NK cytotoxicity (increased to impaired)	Direct uptake/degradation of Aβ; restores microglial phagocytosis; reduces neuroinflammation; meningeal NK-derived IFN-γ promotes memory formation	Chronic activation leads to overproduction of IFN-γ and TNF-α (inversely correlates with cognition); depletion in mouse models reduces neuroinflammation but impairs early protective effects
PD	↑	↑	↑ Infiltrate substantia nigra; colocalize with α-syn aggregates and dopaminergic neurons	CD56^{dim} (blood)	Elevated activation markers; correlates with severity/ progression	Clear α-syn aggregates; likely eliminates autoreactive T cells	α-syn clearance reduces NK cytolytic capacity and IFN-γ secretion, potential dysfunction with chronic activation

by selectively eliminating pathogenic T cells and secreting immunosuppressive factors (IL-10, TGF-β) (Zúñiga et al., 2025). IFN-γ produced by meningeal NK cells has been shown to participate in memory formation in healthy mice (Garofalo et al., 2023). Conversely, circulating NK cells from AD patients exhibit increased secretions of the proinflammatory cytokines IFN-γ and TNF-α, an overproduction inversely correlated with cognitive performance (Solerte et al., 2000). Depletion of NK cells in an AD mouse model has been associated with reduced neuroinflammation, enhanced neurogenesis, and improved cognitive function (Zhang et al., 2020). Those data suggest that while NK cells may exert beneficial effects in the early stages by naturally targeting different pathogenic drivers, their chronic activation could lead to dysfunction and progressively contribute to the pathological burden. Considering that the prevalence of AD strongly correlates with age and that the frequency of CD56^{bright} cells decreases with age (Wang et al., 2025c), one could hypothesize a link between immunoaging-induced NK impairment and the occurrence of AD. Interestingly, increased frequency of NK cells in the cerebrospinal fluid has also been reported in frontotemporal dementia patients, suggesting a potential role in other dementia-inducing neurodegenerative diseases (Busse et al., 2021).

In Parkinson's disease (PD), an α-synucleinopathy, the increased numbers of NK cells, particularly CD56^{dim} [NK1], along with elevated activation markers, have been reported in the blood and substantia nigra of both early- and late-onset PD patients (Earls et al., 2020; Holbrook et al., 2023; Niwa et al., 2012; Tian et al., 2022; Zhang et al., 2024). These changes correlate with disease severity and progression. In PD models, NK cells are increased in the cerebrospinal fluid and infiltrate the affected brain regions, colocalizing with α-syn aggregates and dopaminergic neurons (Guan et al., 2022; Xiong et al., 2024). Analogous to their scavenger role in AD, NK can clear α-syn aggregates, mitigating disease severity. However, this process has been reported to reduce their ability to lyse target cells and secrete IFN-γ. Concurrently, specific reactivity against several products of PD-associated genes (α-syn, PINK1, C9orf72) has been observed in PD patient T cells, driving autoimmune events from the early stages of the disease (Lindestam Arlehamn et al., 2020; Michaelis et al., 2025; Sulzer et al., 2017; Williams et al., 2024). Although direct evidence is lacking in PD, it is plausible that NK cells can limit the harmful adaptive responses as observed in MS and AD. Consistently, murine NK cell depletion promotes disease incidence and severity (Earls et al., 2020; Zúñiga et al., 2025). Since the deposition of α-syn is a central hallmark of multiple system atrophy and Lewy body dementia (McCann et al., 2014), it is possible that NK cells play a similar role in these diseases.

Over the years, our understanding of the constant, dynamic, and reciprocal interactions between the nervous and immune systems has deepened considerably. The traditional neuron-centric vision of neurodegenerative diseases has evolved, and it is now becoming clear that immune dysregulation is a hallmark of many CNS disorders. Drawing parallels between neurodegenerative diseases and classic AIDs offers new hope for the development of effective therapies. A major challenge in CNS drug development remains the brain barrier impermeability, which, even in case of neurodegenerative disease-driven dysfunction, still significantly restricts the CNS biodistribution of molecular therapies to the perivascular space (Lamptey et al.,

2022; Pandit et al., 2020). In this context, the biology of NK cells and their ability to efficiently cross such barriers upon activation have led to the idea that enhancing NK cell recruitment or functions may represent a promising approach to resolve neuroinflammation. Adoptive NK cell transfers are being considered in several indications. Troculeucel (SNK01), a nongenetically modified, cytokine-preconditioned autologous NK cell therapy candidate, displays a highly activated phenotype, secretes immunosuppressive cytokines (IL-10, TGF-β), selectively kills activated T cells, and clears Aβ aggregates *in vitro*. In a phase 1 clinical trial (NCT04678453), SNK01 was administrated intravenously as a single agent to mild- to severe-stage AD patients and was found to be safe and well tolerated, with no severe adverse events reported (Zúñiga et al., 2025). Over the 22-wk study, SNK01 might have demonstrated an early sign of clinical efficacy, as suggested by a stabilization of clinical score and cerebrospinal fluid biomarkers, although longer studies are required to confirm these hypotheses. Following FDA Fast Track designation, SNK01 is currently being evaluated in a phase 2a trial targeting moderate AD stages (NCT06189963). A phase 1 trial (NTC06677710) has also been initiated to evaluate an allogeneic NK cell product (IDP-023) combined with the depleting anti-CD20 antibody ocrelizumab in MS patients. NK cell engagers (NKCE) may also represent promising agents for enhancing the neuroprotective functions of NK cells. They could be engineered to trigger NK cell–mediated killing of autoreactive T cells (Naatz et al., 2025), to potentiate NK cell activation and homeostatic roles (Demaria et al., 2022), and/or to have optimized CNS delivery by targeting receptors involved in transcytosis across barriers (e.g., TfR1, CD98hc, IGRF1) (Alata et al., 2022; Chew et al., 2023; Schumacher et al., 2025), as currently tested in AD (NCT07169578, NCT07170150) and MS (NCT05704361) patients (Schumacher et al., 2025). Although these approaches are still limited, they reflect a changing perspective in which NK cells are recognized as possible contributors in neuroinflammation and neurodegeneration. This opens new therapeutic possibilities in diseases previously thought to be outside the realm of immune modulation.

Thus, NK cells are emerging as regulators at the intersection of neuroinflammation and neurodegeneration. Their ability to eliminate multiple pathogenic drivers such as autoreactive lymphocytes and protein aggregates, and regulate dysfunctional microglia positions them as multifunctional agents. However, their roles are highly context dependent, with protective functions predominating in early disease stages and potential detrimental contributions emerging with chronic activation. The balance between activating and inhibitory signals (exemplified by NKG2C/NKG2D versus NKG2A-HLA-E in MS) represents a critical determinant of outcomes and a possible therapeutic target. As understanding of neuroimmune crosstalk deepens, NK cell–based therapies, including adoptive transfer, genetic modification, and engager platforms, are transitioning from theoretical constructs to possible clinical assets, offering new hope for diseases that have long resisted effective immune-based interventions. The challenge ahead lies in optimizing timing and delivery across brain barriers, and maintaining the delicate balance between neuroprotection and inflammation resolution.

NK cells in AIDs

AIDs affect 10% of the global population, and the incidence and prevalence of many AIDs are increasing worldwide (Scherlinger et al., 2020). AIDs are chronic diseases arising from a complex interplay of genetic, environmental, hormonal, and immunological factors that ultimately lead to a breakdown in immune tolerance. Many details of their pathogenesis and etiology have yet to be elucidated, and further research is needed to address these gaps. As contributors to immune surveillance and regulation via cytotoxic activity and cytokine production, NK cells may play a role in the pathogenesis of AID by promoting inflammation through IFN-γ production, or by alleviating inflammation through the killing of activated T cells (Cerboni et al., 2007; Kilian et al., 2024; Rabinovich et al., 2003) and macrophages (Table 2).

Key features of systemic lupus erythematosus (SLE) include excessive activation of type I IFN pathways, persistent production of diverse autoantibodies targeting nuclear antigens, and the formation of immune complexes in multiple organs, such as the skin, kidneys, lungs, blood, joints, and CNS, resulting in inflammation and tissue damage, exemplified by lupus nephritis. Distinct NK cell subset alterations have been documented (Hervier et al., 2011; Li et al., 2023; Liu et al., 2021). The proportion of $CD56^{dim}$ NK cells is reduced, whereas $CD56^{bright}$ cells are relatively expanded in SLE peripheral blood. Moreover, $CD56^{dim}$ in SLE patients display an activated phenotype, with upregulation of NKp44, NKp46, NKp30, and CD69, alongside downregulation of CD16 and inhibitory KIRs (Hudspeth et al., 2019). The reduced number of circulating NK cells in SLE could be attributed to their migration from the peripheral blood to the damaged tissue. This possibility is supported by the increased expression of the NKG2D ligand MICA in kidneys of patients with lupus nephritis paralleling greater infiltration of activated NK cells into glomeruli in murine SLE models (Spada et al., 2015). NK cells of SLE patients demonstrated reduced cytotoxicity, while the production of IFN-γ remained elevated (Hervier et al., 2011; Lin et al., 2017; Liu et al., 2021; Lu et al., 2022). Patients with SLE present higher levels of circulating IL-15 and an increased proportion of NK cells expressing the proliferation marker Ki67, which are strongly correlated with clinical severity (Hudspeth et al., 2019; Lin et al., 2017). Mechanistically, a recent study has revealed that mitochondrial dysfunction and defective mitophagy are key drivers of NK cell abnormalities in SLE (Fluder et al., 2025, *Preprint*). Alongside, tissue-resident $NKp46^{+}$ group 1 ILC1s appear to be key amplifiers of kidney inflammation in lupus nephritis. These cells promote macrophage expansion and epithelial cell injury through GM-CSF production, and blocking or deleting NKp46 prevents tissue damage, revealing a new mechanism driving organ injury in AID (Biniaris-Georgallis et al., 2024). Further research using single-cell RNA sequencing on peripheral blood and kidney or skin tissue from individuals with SLE could yield a clearer understanding of the contribution of NK cells to disease pathogenesis.

Rheumatoid arthritis (RA) is a highly prevalent chronic inflammatory disorder characterized by persistent synovial inflammation, progressive cartilage degradation, and bone erosion. While autoimmune T and B cell responses are

Table 2. **NK cell characteristics in AIDs**

Disease	Circulating NK cells	Tissue NK cells	Predominant phenotype	Activation/functional status	Protective mechanisms	Detrimental effects
SLE	↓	↑ (kidneys, glomeruli)	CD56^{bright} (blood)	Activated phenotype, upregulation of NCRs; downregulation of CD16 and KIRs (blood); upregulation of MICA (kidneys); reduced cytotoxicity; increased IFN-γ production	Not well defined	Tissue-resident NKp46^{+} ILC1s amplify kidney inflammation through GM-CSF production
RA	↑	↑ (synovial fluid)	CD56^{bright} (synovial fluid)	Activated phenotype; reduced cytotoxicity; increased IFN-γ production (synovial NK cells)	Not well defined	Likely promotes synovial inflammation through IFN-γ and TNF-α; osteoclastogenesis and bone destruction via RANKL and M-CSF expression; exacerbates inflammation through GM-CSF production
pSS	↓	↑ (salivary glands)	CD56^{bright} (blood)	IFN-γ secretion (via interaction with B7-H6 expressed on salivary gland epithelial cells)	Tissue-resident NK shield target cells from T cell–mediated cytotoxicity	NK infiltration correlates with glandular inflammation; contributes to ectopic lymphoid structures formation; amplifies autoimmune responses in the glands via IFN-γ production
SSc	Debated/vary with stage	Not well defined	Not well defined	Not well defined	Not well defined	Not well defined
T1D	↓	↑ (pancreatic islets)		Activated phenotype, spontaneous IFN-γ at early stages; dysfunctional state at later stages	Secretion of immunosuppressive cytokines and killing of autoreactive T cells	Promotes adaptive autoimmune response and β cell destruction through IFN-γ production and NKp46-dependent cytotoxicity

predominant, innate immune cells have also been implicated in RA pathogenesis. Several studies have demonstrated that patients with RA have higher levels of NK cells in their peripheral blood than healthy controls. However, these NK cells have reduced cytotoxic activity (Fathollahi et al., 2021; Lin et al., 2020; Zhao et al., 2025). Analyses of synovial fluid consistently revealed an enrichment of CD56^{bright} cells (Coyle et al., 2024; Dalbeth and Callan, 2002; Pridgeon et al., 2003). These synovial NK cells frequently exhibit increased activation markers, production of inflammatory cytokines (IFN-γ and TNF-α), and impaired cytotoxicity (Yamin et al., 2019); phenotypic and functional features that have been inversely associated with disease remission (Coyle et al., 2024). NK cells within RA synovial tissues express both RANKL and M-CSF, which may contribute to osteoclastogenesis and subsequent bone destruction. Depletion of NK cells from mice before the induction of collagen-induced arthritis reduces the severity of subsequent arthritis and almost completely prevents bone erosion (Söderström et al., 2010). Another murine study in the collagen-induced arthritis model found that NK cell infiltration in joints correlated positively with arthritis score, histopathology, and bone destruction. Adoptive transfer of NK cells increased arthritis severity, while NKp46 knockout had no effect on incidence/severity (Wu et al., 2022). Finally, in an autoantibody-mediated inflammatory arthritis mouse model, synovial NK cells were shown to produce GM-CSF and exacerbate inflammation by promoting a neutrophil infiltrate (Louis et al., 2020).

In primary Sjögren's syndrome (pSS), the lacrimal and salivary glands are the main organs affected. The presence of autoantibodies and hypergammaglobulinemia is a key feature of this condition, highlighting the important role of B cells in its pathogenesis. However, accumulating evidence indicates significant alterations within the innate immune system, particularly involving NK cells. Several studies have demonstrated that patients with pSS exhibit lower levels of circulating NK cells than healthy controls (Cheng et al., 2023; Davies et al., 2017; Ming et al., 2020; Shi et al., 2022). Like in SLE, the proportion of CD56^{dim} cells is reduced, while the CD56^{bright} subset is increased in the peripheral blood of pSS patients. Salivary glands from pSS patients show NK cell enrichment, which correlates with glandular inflammation. Interactions between NKp30 and B7-H6, where B7-H6 is expressed by dendritic cells and salivary gland epithelial cells, can induce IFN-γ secretion (Rusakiewicz et al., 2013). These data suggest a mechanism by which NK cells may foster local immune activation and contribute to the formation of ectopic lymphoid structures (Pontarini et al., 2021). Clinical observations indicate that belimumab, an antibody blocking the B cell–activating factor BAFF, is less effective in patients with a high frequency of NK cells in their peripheral blood and glandular tissue, suggesting that elevated NK infiltration may indicate a poorer response to treatment (Seror et al., 2015). In a pSS

mouse model, salivary gland NK cells were found to amplify autoimmune responses within the glands via IFN-γ production, thereby impairing gland function. Conversely, tissue-resident NK cells appeared to exert protective effects, shielding target cells from T cell–mediated cytotoxicity (Sato et al., 2022).

Systemic sclerosis (SSc) is a multifaceted autoimmune connective-tissue disorder hallmarked by collagen and extracellular matrix deposition, leading to fibrosis of the skin, lungs, heart, and gastrointestinal tract. Additionally, it is associated with pronounced microvascular stenosis and the presence of disease-specific autoantibodies that reflect immune dysregulation driving fibrotic progression. The degree of NK cell alterations in the peripheral blood of patients with SSc remains debated (Almeida et al., 2015; Benyamine et al., 2018; Gumkowska-Sroka et al., 2019; Guo et al., 2025; Van Der Kroef et al., 2020). The discrepancies could come from the stage of the disease, as an increased frequency and number of NK cells have been reported in diffuse cutaneous SSc, whereas they were normal in limited cutaneous SSc in the same cohort.

Type 1 diabetes (T1D) is a chronic disease resulting from autoimmune destruction of pancreatic insulin-producing β cells. Multiple lines of evidence implicate NK cells in both the initiation and the progression of T1D. Under homeostatic conditions, NK cells are present at low levels in the pancreas (Radenkovic et al., 2017; Shi et al., 2011); however, their number increases in diabetes-prone conditions from the early stages of the disease. In patients with T1D, peripheral NK cell counts and frequencies have been repeatedly reported to be reduced compared with healthy individuals (Gomez-Muñoz et al., 2021; Qin et al., 2011; Sieniawska et al., 2023), a change suggested as a potential reflect of their extravasation into the pancreas. Consistently, NK cells are among the first immune cells to invade the pancreas in mice, localizing to islets before T cells (Brauner et al., 2010). From the prediabetic stages, NK cells locally acquire an activated phenotype and display spontaneous IFN-γ secretions and progressively adopt a dysfunctional/hyporesponsive state (Brauner et al., 2010; Qin et al., 2011). Mechanistically, NK cells play a multifaceted role in T1D pathogenesis. They contribute to disease progression by promoting the adaptive autoimmune response and β cell destruction through both the secretion of T cell–stimulating IFN-γ (Alba et al., 2008; Feuerer et al., 2009; Poirot et al., 2004) and NKp46-dependent direct cytotoxicity (Gur et al., 2011). Additionally, NKG2D blockade limits T1D onset in mouse models, although it remains uncertain whether these effects are mediated by autoreactive NKG2D$^+$ T and/or NK cells (Ogasawara et al., 2004; Van Belle et al., 2013). NK cells have been shown to recognize enterovirus-infected β cells, implicating them in virus-triggered T1D onset (Dotta et al., 2007; Flodström et al., 2002). Conversely, NK may also exert protective roles via the secretion of immunosuppressive cytokines and the killing of autoreactive T cells, a property likely to be decreased as they lose their cytotoxic capabilities during T1D progression (Qin et al., 2011; Yoon Kim and Kwon Lee, 2022). Longitudinal blood transcriptomics analyses from the TEDDY cohort identified strong enrichment of NK cell–specific transcripts in association with the development of islet autoimmunity in both patients developing autoantibodies to insulin (IAA) and glutamic acid decarboxylase, and with progression to diabetes in IAA patients (Xhonneux et al., 2021). Similarly, NK cell signatures have been associated with the rate of decline in C-peptide, a marker of functional β cell, in the INNODIA cohort (Armenteros et al., 2024) and with patient responses to teplizumab, a Fc-silenced anti-CD3 antibody in the AbATE study (Sassi et al., 2025). Further studies are required to fully elucidate the role of NK cells in T1D pathogenesis.

There is even less evidence for the role of NK cells in other systemic AIDs such as anti-neutrophil cytoplasmic antibody-associated vasculitis (Fuchs et al., 2022) and inflammatory myopathies. Overall, there is some evidence suggesting that NK cells may amplify inflammation by releasing cytokines and recruiting or activating other immune cells. At the same time, they could play a protective role by eliminating autoreactive T and B lymphocytes. However, mechanistic data are still needed to definitively clarify the exact role of NK cells in AID.

Despite the heterogeneity of AIDs, several unifying patterns of NK cell alterations thus emerge across conditions. The frequent reduction of circulating NK cells suggests active tissue migration rather than systemic depletion, as evidenced by their enrichment in target organs where they can contribute to local pathology. A consistent phenotypic shift characterized by decreased CD56^{dim} and relatively expanded CD56^{bright} populations in peripheral blood suggests a common underlying mechanism of NK cell dysregulation. Notably, a functional dissociation is observed across multiple AIDs, wherein NK cells exhibit impaired cytotoxicity yet maintain or increase their capacity for inflammatory cytokine production, particularly IFN-γ. This imbalance may contribute to sustained inflammation while diminishing their potential regulatory function of eliminating autoreactive lymphocytes. Additionally, tissue-resident NK cells and related ILC1s play distinct and often pathogenic roles within affected organs, amplifying local immune responses through cytokine secretion and immune cell recruitment. The correlation between NK cell alterations and disease severity or treatment responses in conditions such as SLE, pSS, and T1D underscores their clinical relevance. Collectively, these findings highlight a role of NK cells, yet incompletely understood, as contributors to autoimmune pathogenesis warranting further mechanistic investigation to clarify their potential as therapeutic targets or biomarkers of disease activity.

Although the pathogenesis of systemic AIDs is complex, part of them seem to rely on autoantibody-producing cells. Indeed, B cell–targeting therapeutics have produced positive clinical outcomes in certain cases, such as anti-neutrophil cytoplasmic antibody-associated vasculitis. Rituximab, a chimeric anti-CD20 monoclonal antibody, is commonly used for these conditions (Hauser et al., 2008; Stone et al., 2010), and more recently, obinutuzumab, a humanized Fc-optimized monoclonal antibody, has been approved by the FDA following positive results from a phase III clinical trial in patients with lupus nephritis (Furie et al., 2025). However, the most promising results to date have emerged from the field of cell therapy. Building on their successes in oncology, T cell–mediated therapies such as CAR-T cells could transform the treatment of B cell–mediated AIDs. Autologous CD19-targeted CAR-T cell therapies, originally developed for oncological conditions, have been administered to

patients with refractory systemic AIDs, with early-phase clinical cohorts reporting drug-free remission (Auth et al., 2025; Fischbach et al., 2024; Merkt et al., 2024; Minopoulou et al., 2025; Müller et al., 2024; Shu et al., 2025). Other autologous CAR-T cell products that target the plasma cell antigen BCMA, or BCMA and CD19, as well as off-the-shelf allogeneic products, are also showing promising results (Hu et al., 2025; Qin et al., 2025; Wang et al., 2024). Strategies to overcome the limitations of cell therapy were engineered using T cell–targeted lipid nanoparticles to deliver CD19 CAR mRNA, and are now beginning to show their first encouraging results (Wang et al., 2025a). T cell engagers offer a promising alternative to cell therapies, as they are off-the-shelf assets that do not require preconditioning regimens. Current clinical evaluations have yielded encouraging results in RA and SSc (Bucci et al., 2024; Bucci et al., 2025; Hagen et al., 2024; Subklewe et al., 2024). In this context, the biology of NK cells positions them as possible candidates for such therapeutic strategies. AB-101, an allogeneic nongenetically modified NK cell product, is currently assessed alone or in combination with B cell–depleting agents (rituximab or obinutuzumab) in multiple AIDs such as SLE, RA, pSS, and SSc (NCT06265220, NCT06581562, NCT06991114). A recent report indicates that iPSC-derived CAR-NK cells may offer distinct advantages over T cell–centric therapies in the treatment of AIDs. In a proof-of-concept case of diffuse cutaneous SSc, administration of an allogeneic dual-targeting CAR-NK product (CD19 and BCMA) induced rapid and durable clinical improvement, accompanied by a profound resetting of the B cell compartment and reduction in autoantibody titers (Wang et al., 2025b). Compared with CAR-T cells, CAR-NK approaches are inherently safer in the allogeneic setting, with a markedly reduced risk of cytokine release syndrome, immune effector cell–associated neurotoxicity, and graft-versus-host disease, thereby improving the therapeutic risk–benefit profile in nonmalignant settings. Their derivation from iPSCs also enables scalable, standardized, and truly off-the-shelf manufacturing, overcoming the logistical and economic barriers of autologous CAR-T production. Dual targeting of both B cells and long-lived plasma cells addresses a key limitation of CD19-directed strategies and may yield deeper and more durable immune modulation. Moreover, the CAR-NK platform supports multiplex genetic engineering, including edits that improve persistence, prevent host rejection, and incorporate safety switches, providing a level of programmability and versatility difficult to achieve with individualized CAR-T products. Collectively, these features position CAR-NK therapies as an interesting next-generation strategy for broad application across antibody-mediated AIDs, combining the efficacy of targeted immune depletion with improved safety and accessibility. These data are supported by an exploratory clinical study investigating anti-CD19 CAR-NK cells for the treatment of relapsed refractory SLE patients, which has demonstrated promising outcomes, including B cell immune reset and a good safety profile (NCT06010472) (Gao et al., 2025).

NK cells in solid organ allografts

Organ transplantation necessitates a delicate balance within the immune system: it must maintain tolerance toward genetically distinct grafts yet remain efficient against pathogens. Historically perceived as peripheral participants, NK cells are emerging as pivotal agents influencing chronic rejection of solid organ allografts. In the context of both hematopoietic and solid organ transplantation, mismatches in MHC molecules between donor and recipient can disrupt the inhibitory signals controlling NK cells. This triggers NK cell–mediated cytotoxicity through a "missing-self" mechanism, i.e., the absence of interaction between MHC class I molecules and their cognate inhibitory receptors such as KIR and NKG2A, expressed on NK cells (Kärre, 2002). Additionally, NK cells can migrate toward grafts following inflammatory chemokine signals (such as CXCL9 and CXCL10) and adaptively modulate their phenotype within the transplant environment. Finally, NK cells can also recognize stressed cells within the allograft through NKG2D and NCRs, a mechanism that may contribute to the elimination of the solid organ graft, even in the absence of donor-specific antibodies against the allograft. In addition, in sensitized solid organ transplant recipients, preexisting donor-specific antibodies coat the graft endothelium. Patient NK cells, through CD16, can then exert antibody-mediated rejection (AMR) via ADCC (Koenig et al., 2021; Thaunat et al., 2025). This activity significantly contributes to microvascular inflammation, complement deposition, and endothelial cell damage. Histological and transcriptomics data have robustly associated infiltrating $CD16^{+}$ NK cells with severe microvascular injury within graft tissues.

CD38, a molecule expressed by plasma cells and certain NK cell subsets, has become a target of therapeutic interest beyond hematologic malignancies. Within transplantation, CD38 targeting simultaneously curbs alloantibody production and dampens NK-mediated ADCC. A landmark phase II trial that assessed the efficacy of felzartamab, a CD38-depleting antibody, among kidney transplant recipients with chronic AMR at least 6 mo after transplantation demonstrated a marked histological reversal of AMR (Mayer et al., 2024). Moreover, significant reductions were observed in microvascular inflammation scores, molecular rejection signatures, and donor-derived cell-free DNA, indicative of reduced graft injury. Remarkably, these therapeutic effects correlated with notable peripheral NK cell depletion. Safety profiles indicated predominantly mild-to-moderate infusion reactions, with fewer severe adverse events and graft losses compared with placebo. Importantly, the response durability was evident at 1 year, with only three initial responders experiencing AMR recurrence. From a mechanistic perspective, the felzartamab trial provides compelling evidence that depletion of CD38-positive NK cells and plasma cells substantially mitigates ADCC-driven endothelial injury. Thus, it delivers unprecedented mechanistic validation, establishing NK cells as direct contributors to late-stage AMR pathology and highlights critical insights relevant to transplant immunobiology. Firstly, NK cells actively drive late-stage AMR, as their targeted depletion results in histological recovery. Secondly, concurrent inhibition of B cell–derived alloantibodies and NK cell effector functions offers synergistic therapeutic advantages. Long-term monitoring of infections, malignancies, and immune reconstitution will be critical as larger phase III trials progress. Future research directions should emphasize refined NK cell

characterization of CD38⁺ NK populations implicated in graft rejection. Furthermore, combining anti-CD38 therapy with IL-6 antagonists, complement inhibitors, or Fc receptor modulators may optimize therapeutic strategies, enhancing graft tolerance without significantly compromising overall immunity. Identifying predictive biomarkers, such as baseline CD38 expression on infiltrating NK cells, could further refine patient selection.

Overall, NK cells have transitioned from innate immune guardians to mediators of transplant-associated immune responses, positioning them simultaneously as key pathogenic agents and promising therapeutic targets.

Conclusion and perspectives

NK cells have long been studied in the context of infection and cancer. New therapeutic technologies such as NK cell engagers and engineered NK cells are paving the way for precision NK cell–based immunotherapies. Although primarily developed for oncology, these technologies may be adapted to treat noncancerous diseases with high unmet needs in a broader range of diseases, including viral infections, neurodegeneration, autoimmunity, and transplantation. Moving forward, critical questions remain. Identifying disease-relevant NK cell subsets, selectively targeting or expanding them, and safely monitoring their effects in patients will be essential for clinical translation. Nonetheless, the evolving landscape of NK cell research suggests that these innate lymphocytes should be considered, not only as defenders against infection and malignancy, but also as modulators of chronic immune-mediated conditions.

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