

Natural Killer Cells in Kidney Transplantation: Dual Role in Allograft Injury and Immune Adaptation

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Abstract

Kidney transplantation is the optimal treatment for end-stage renal disease, yet long-term graft survival remains limited by allograft rejection. While T and B cells and donor-specific antibodies (DSA) have been the main focus, accumulating evidence indicates that natural killer (NK) cells play a significant dual role in both graft injury and immune adaptation, including in DSA-negative rejection. This narrative review summarizes current knowledge on the dual role of NK cells in kidney transplantation, with emphasis on antibody-independent mechanisms, adaptive NK-cell subsets, and their potential as biomarkers of graft outcome. NK cells are highly heterogeneous, consisting of CD56^{bright} and CD56^{dim}CD16 subsets. Cytomegalovirus infection promotes expansion of adaptive NKG2C⁺CD57⁺ cells with memory-like features. In rejection, NK cells act through both antibody-dependent cellular cytotoxicity and antibody-independent pathways, such as “missing-self” recognition via killer immunoglobulin-like receptors (KIR)/human leukocyte antigen (HLA) mismatch and release of the killer-specific secretory protein of 37 kDa (Ksp37). Specific NK subsets are associated with microvascular inflammation and graft loss even in the absence of DSA. In contrast, NK cells support tolerance by killing donor dendritic cells and activated T cells, producing interleukin (IL)-10 and transforming growth factor- β (TGF- β), and undergoing reeducation, gradually shifting from a cytotoxic to a regulatory phenotype. NK cells exert a dual, often opposing role in kidney transplantation, mediating both allograft injury and immune tolerance. Better understanding of their plasticity may enable new biomarkers and NK-targeted therapies to improve long-term graft survival.

Keywords

Natural killer cells • NK • Kidney transplantation • Allograft rejection • Ischemia-reperfusion injury • Immune tolerancenc

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1. Introduction

Kidney transplantation remains the treatment of choice for patients with end-stage renal disease. Thanks to advances in surgical techniques and modern immunosuppressive therapies, most recipients achieve not only a significant prolongation of life but also a marked improvement in quality of life (Babich et al. 2026). Current 1-year post-transplant survival rates reach approximately 95% (Meier-Kriesche et al. 2001; Babich et al. 2026). Nevertheless, a substantial proportion of patients still do not achieve such favorable long-term outcomes. Complications result from both recipient-related factors (comorbidities, age, and adherence) and donor-related factors. The latter, including incompletely understood mechanisms of the alloimmune response, can lead to acute or chronic graft rejection and underscore the need for further intensive research into the pathogenesis of graft dysfunction (Pontrelli et al. 2020; Poggio et al. 2021; Ruan et al. 2024). The traditional theory of allograft rejection has focused primarily on the role of T and B lymphocytes and anti-HLA

antibodies (Halloran 2010; Clatworthy 2011). However, this approach fails to explain all cases of allograft injury, particularly those without detectable donor-specific antibodies (DSA) or classic lymphocytic infiltrates (Delville et al. 2016). Consequently, in recent years, increasing attention has been directed toward the innate immune system, especially natural killer (NK) cells. Recent studies demonstrate that NK cells serve as important mediators of both graft injury and immunological adaptation to the transplanted organ (Pontrelli et al. 2020; Ruan et al. 2024).

NK cells are present in various tissues, including the skin, liver, lungs, and kidneys. They are particularly enriched in the liver, where they constitute approximately 25%–30% of intrahepatic lymphocytes (Paul and Lal 2017). Unlike T lymphocytes, NK-cell activation does not require prior antigen presentation by antigen-presenting cells (APCs). This allows them to mount a rapid, innate immune response. For many years, NK cells were regarded primarily as cytotoxic effector cells. However, recent research has highlighted their remarkable phenotypic and functional plasticity (Ruan et al. 2024). In peripheral blood, two main subpopulations predominate: CD56^{bright} (approximately 5%–10%) and CD56^{dim} (approximately 90%) (Van Acker et al. 2017). Furthermore, under conditions of chronic antigenic stimulation—particularly cytomegalovirus (CMV) infection—adaptive NK cells with the NKG2C⁺ and CD57⁺ phenotype can emerge. These cells exhibit memory-like properties, representing a form of

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immunological memory within the innate immune system (Gumá et al. 2004; Ruan et al. 2024).

NK cells exhibit a clear functional duality in the context of kidney transplantation. On the one hand, they can contribute to allograft injury through direct cytotoxicity as well as amplification of the adaptive immune response. On the other hand, they may promote immunological tolerance, among others, by eliminating activated T lymphocytes or donor-derived dendritic cells and through interactions with regulatory cells (Pontrelli et al. 2020). Of particular importance are data indicating the involvement of specific NK cell subsets in graft dysfunction independently of the presence of DSA (Ruan et al. 2024).

The dynamics of changes in the phenotype and function of NK cells following kidney transplantation remain poorly understood; however, a comprehensive assessment using flow cytometry may yield new biomarkers of immune adaptation (Ruan et al. 2024).

2. Aim

The aim of this narrative review is to summarize current knowledge on the dual role of NK cells in kidney transplantation, with emphasis on antibody-independent mechanisms, adaptive subsets, and their potential as biomarkers of graft outcome.

3. Search Strategy

Literature for this narrative review was identified through systematic searches in PubMed, Scopus, and Web of Science up to May 2026 using combinations of terms, such as “NK cells,” “natural killer cells,” “KIR,” “NKG2C,” “kidney transplantation,” and “allograft rejection.” Relevant articles were selected, and additional studies were identified through snowballing (manual screening of reference lists of key papers and reviews).

4. The Heterogeneity and Plasticity of NK-Cell Subpopulations

NK cells constitute a highly heterogeneous population of lymphocytes, whose phenotypic and functional diversity significantly influences the alloimmune response following kidney transplantation (Pontrelli et al. 2020; Ruan et al. 2024).

Two major subpopulations predominate in peripheral blood. The CD56^{bright} subpopulation accounts for approximately 5%–10% of circulating NK cells and is characterized by high expression of the inhibitory receptor NKG2A, low expression of CD16, and potent cytokine-producing capacity, particularly interferon (IFN)- γ (Van Acker et al. 2017). These cells primarily exert regulatory and immunomodulatory functions, including interactions with dendritic cells (Ruan et al. 2024). In kidney transplantation, an increased proportion of CD56^{bright} cells, as well as a high CD56^{bright}/CD56^{dim} ratio, has been associated with acute cellular rejection (Xu et al. 2019).

Although CD56^{bright} NK cells express high levels of the inhibitory receptor NKG2A, their potent Interferon-gamma (IFN- γ) secretion can predominate in the transplant setting, promoting T-cell recruitment and inflammation and thereby associating circulating CD56^{bright} cells with increased risk of cellular rejection (Kildey et al. 2019; Xu et al. 2019). The net functional outcome of this dual phenotype remains context-dependent and is still incompletely understood.

In contrast, the CD56^{dim} CD16⁺ subpopulation, which comprises approximately 90% of NK cells in peripheral blood, displays high cytotoxic activity, including strong antibody-dependent cellular cytotoxicity (ADCC) (Le Garff-Tavernier et al. 2011; Van Acker et al. 2017). The alloreactivity of these cells against the allograft depends largely on the expression of killer immunoglobulin-like receptors (KIRs) and the process of “licensing” (education) (Poli et al. 2009; Foley et al. 2011; Le Garff-Tavernier et al. 2011).

In addition, CMV infection—the most common viral complication after kidney transplantation—plays a key role in driving the expansion of adaptive NK cells. Under chronic antigenic stimulation by CMV, there is a significant expansion of the NKG2C⁺CD57⁺ NK-cell population, which acquires features of immunological memory – a phenomenon considered unique to the innate immune system (Hadaya et al. 2008; Ruan et al. 2024).

The recipient’s KIR/HLA genotype has been shown to influence the risk of CMV infection. In patients with active infection, NK cells exhibit a characteristic expansion with increased expression of the activating receptors NKG2C and NKG2D, accompanied by a transient reduction in IFN- γ production during the acute phase. Consequently, the increased presence of adaptive NK cells in the late post-transplant period primarily reflects long-term remodeling of the immune response aimed at effective antiviral defense, rather than the induction of tolerance toward the allograft (Hadaya et al. 2008).

In addition, the activity of NK cells is tightly regulated by inhibitory receptors, among which NKG2A/CD94 plays a particularly important role as an immune checkpoint molecule (Kaulfuss et al. 2023). NKG2A controls NK-cell expansion capacity by limiting both excessive proliferation and activation-induced cell death, thereby maintaining the balance between effective antiviral response and prevention of overactivation.

NKG2A is a key inhibitory receptor that recognizes human leukocyte antigen E (HLA-E) on graft cells and suppresses NK-cell cytotoxicity (Kaulfuss et al. 2023). HLA-E exhibits limited polymorphism, primarily represented by the alleles HLA-E*01:01 and HLA-E*01:03, which differ in cell-surface expression levels and peptide-binding affinity. These differences influence the strength of inhibitory signaling through NKG2A on both NK cells and CD8⁺ T cells. In the setting of allogeneic hematopoietic stem cell transplantation, HLA-E*01:03 homozygosity has been associated with a

stronger graft versus leukemia effect mediated by NK cells and reduced relapse rates (Hosseini et al. 2013). Similar differences in HLA-E-NKG2A affinity, previously observed to modulate inhibitory signaling in both NK cells and CD8⁺ T cells in the context of COVID-19 (Hosseini et al. 2023), may also influence the balance between alloreactivity and tolerance in solid organ transplantation. Early after transplantation, an increased proportion of CD56^{bright} NK cells with high NKG2A expression and low KIR levels is often observed, resulting in impaired cytotoxic function. These abnormalities typically normalize within 1 year as CD56^{bright} cells differentiate into the CD56^{dim} subset, accompanied by decreased NKG2A expression and recovery of NK-cell cytotoxicity (Ghasemzadeh et al. 2016). NK cells also mediate the “missing-self” response by recognizing and eliminating cells with low or absent HLA class I expression. To counteract this, novel therapeutic approaches using selective agonists of inhibitory receptors, that is, NKG2A and KIRs, are being developed. These strategies effectively suppress NK-cell-mediated rejection, particularly in the context of HLA-deficient induced pluripotent stem cell-derived grafts (Hiura et al. 2025). Circulating and graft-infiltrating NK-cell phenotypes frequently show an inverse relationship, whereby a decrease in specific subsets in peripheral blood correlates with their enrichment within the allograft (Kildey et al. 2019; Ruan et al. 2024). Beyond the well-studied KIR and NKG2 families, the balance between activating natural cytotoxicity receptors (NCRs: NKp30, NKp44, NKp46) and inhibitory receptors further shapes NK-cell reactivity during transplantation, tipping the scales toward either graft injury or regulatory adaptation (Pontrelli et al. 2020; Ruan et al. 2024). The main phenotypic markers, functional properties, and clinical relevance of the major NK-cell subpopulations in the context of kidney transplantation are summarized in Table 1.

5. Role of NK Cells in Ischemia-Reperfusion Injury

Ischemia-reperfusion injury (IRI) is an inevitable early event in kidney transplantation that triggers a sterile inflammatory response and significantly contributes to delayed graft

function and subsequent alloimmune activation (Ma et al. 2023; Troise et al. 2025; Horowitz and Heeger 2026). NK cells are rapidly recruited to the injured graft within hours after reperfusion. They recognize stress-induced ligands on damaged tubular epithelial cells (e.g., via the NKG2D receptor) and exert direct cytotoxicity, thereby amplifying initial tissue damage (Ma et al. 2023; Fuhrmann et al. 2024). Recent evidence indicates that NK cells play a pathogenic role in IRI through both contact-dependent killing of tubular epithelial cells and secretion of pro-inflammatory mediators that promote neutrophil recruitment and activation. NK cells facilitate neutrophil infiltration into the injured graft, thereby amplifying microvascular dysfunction. Neutrophils subsequently generate reactive oxygen species (ROS), a central effector mechanism of reperfusion injury that causes oxidative stress and tubular cell death. Thus, the NK-cell-neutrophil axis and downstream ROS production constitute an important early innate pathway linking ischemia-reperfusion to subsequent alloimmune activation. Strategies targeting NK-cell activation pathways (such as dual mechanistic target of rapamycin (mTOR) and calcineurin inhibition) have shown promise in mitigating these effects in preclinical models (Ma et al. 2023; Tsao et al. 2024; Troise et al. 2025; Horowitz and Heeger 2026). Ultimately, NK-cell activation during IRI represents an important early mechanism of graft injury that is largely independent of adaptive immunity. A better understanding of these processes, as reviewed by Horowitz and Heeger (2026), may open new therapeutic avenues to limit early graft damage and improve long-term outcomes.

6. The Role of NK Cells in Allograft Rejection

NK cells play a significant role in the pathogenesis of kidney allograft injury and rejection (Pontrelli et al. 2020). They contribute through both antibody-dependent mechanisms, primarily ADCC, and antibody-independent pathways. This involvement is supported by multiple lines of evidence from immunohistochemical, transcriptomic, and functional studies. DSA contribute to allograft rejection primarily through antibody-mediated mechanisms. In antibody-mediated rejection

Table 1. The main NK-cell subpopulations and their role in kidney transplantation

Subpopulation	Proportion in blood	Key markers	Main function	Role in kidney transplantation
CD56 ^{bright}	5%–10%	NKG2A, CD16	Cytokine production (IFN- γ , IL-10, TGF- β)	Regulatory, pro-tolerogenic
CD56 ^{dim} CD16 ⁺	~90%	KIR, CD16	Cytotoxicity, ADCC	Mediator of ABMR and acute rejection
Adaptive NK	Variable	NKG2C, CD57, KIR	Memory-like, enhanced cytotoxicity	Antiviral defense + possible chronic alloreactivity

ABMR, acute antibody-mediated rejection; ADCC, antibody-dependent cellular cytotoxicity; IFN, interferon; IL, interleukin; KIR, killer immunoglobulin-like receptor; NK, natural killer; TGF, transforming growth factor.

(AMR), DSA bind to HLA antigens on graft endothelial cells, triggering complement activation and, importantly, ADCC. In ADCC, the Fc portion of DSA engages the CD16 (FcγRIII) receptor on CD56^{dim} NK cells, leading to their activation, degranulation, and direct killing of antibody-coated target cells (Kildey et al. 2019; Pontrelli et al. 2020). This DSA-NK-cell interaction is a key effector pathway in microvascular inflammation (MVI) and chronic graft injury, even when complement deposition is limited.

Kidney allograft rejection is traditionally classified into two main types: T cell-mediated rejection (TCMR) and AMR (Pontrelli et al. 2020). In TCMR, an increased proportion of CD56^{bright} NK cells is commonly observed in peripheral blood. In contrast, AMR is associated with the accumulation of both CD56^{bright} and CD56^{dim} NK-cell subsets within the graft tissue (Kildey et al. 2019). Notably, CD56^{bright} NK cells can actively promote the pathological immune response in TCMR through the production of pro-inflammatory cytokines, such as tumor necrosis factor-α and IFN-γ (Kildey et al. 2019).

In chronic active antibody-mediated rejection (cAMR), MVI plays a central role and is characterized by inflammatory cell infiltration in glomerular and peritubular capillaries (Diebold et al. 2025). Typical histological features include glomerular basement membrane double contours (cg) and multilayering of peritubular capillary basement membranes. According to the Banff 2022 classification, a diagnosis of cAMR requires the presence of DSA and C4d deposition. However, MVI can also occur in DSA-negative and C4d-negative cases. These findings highlight the limitations of purely morphological assessment, which is why molecular diagnostics are increasingly used to detect even subclinical forms of antibody-mediated injury.

Importantly, recent high-dimensional analyses have revealed a distinct pathway of antibody-independent allograft injury mediated by NK cells. Ruan et al. (2024) demonstrated that specific NK-cell subsets (particularly those expressing defined combinations of KIRs and NKG2A) exhibit heightened alloreactivity that persists despite immunosuppression. Pretransplant release of Ksp37 by these cells was associated with worse long-term graft function, and its intragraft expression predicted graft loss even in biopsies without overt histological rejection (Ruan et al. 2024). These findings strongly support the existence of a clinically relevant, DSA-independent mechanism of NK-mediated graft injury.

Beyond antibody-dependent mechanisms, HLA class I disparity between donor and recipient can directly activate recipient NK cells through the “missing-self” recognition pathway. Inhibitory KIRs on NK cells normally recognize self-HLA class I ligands. When donor endothelial cells lack the appropriate HLA ligands for the recipient’s inhibitory KIRs, NK cells perceive this as “missing self” and become activated, leading to endothelial injury. In a study of kidney transplant recipients with MVI but no detectable DSA, 65.1% exhibited a genetically

predicted mismatch between donor HLA class I and recipient inhibitory KIRs (Lebraud et al. 2022). This KIR-HLA ligand incompatibility enabled NK-cell-mediated allorecognition and damage to donor endothelium independently of antibodies. These findings highlight KIR-HLA mismatch as an important, DSA-independent risk factor for NK-cell-driven allograft injury.

From a prognostic perspective, serial monitoring of circulating NK-cell phenotypes may provide early signals of graft dysfunction. However, because peripheral blood levels of certain subsets are often inversely related to their accumulation in the allograft, combined assessment of circulating and graft-infiltrating NK profiles is likely to offer superior predictive value for long-term outcomes, including MVI and graft loss independent of DSA (Kildey et al. 2019; Ruan et al. 2024; Horowitz and Heeger 2026).

Experimental evidence indicates that NK-cell depletion can improve allograft outcomes. In preclinical models, antibody-mediated NK-cell depletion combined with cyclosporine A significantly prolonged kidney graft survival and improved function (Ashraf et al. 2019). These observations suggest that targeted NK-cell depletion or functional inhibition may represent a promising strategy in selected high-risk transplant settings.

In summary, NK cells contribute to kidney allograft rejection through both antibody-dependent (ADCC, DSA/C4d-positive cAMR) and antibody-independent (KIR-mediated, Ksp37-associated) pathways. Their activity is incompletely suppressed by current immunosuppression and correlates with long-term graft loss. Recognizing NK cells as independent effectors of chronic rejection may open new avenues for biomarker development and targeted therapy.

7. The Role of NK Cells in Promoting Immune Tolerance and Adaptation

While NK cells are widely recognized for their contribution to allograft injury, accumulating evidence highlights their functional duality and potential role in promoting immune tolerance and long-term adaptation to the transplanted kidney. Far from being solely cytotoxic effectors, NK cells can exert immunoregulatory effects that may facilitate graft acceptance. Key mechanisms include the selective elimination of donor-derived APCs (particularly dendritic cells), which limits direct allorecognition by recipient T cells, as well as indirect modulation of the adaptive immune response through interactions with regulatory T cells (Tregs). These tolerogenic properties position NK cells as active participants in the complex process of immune adaptation following transplantation. Understanding this regulatory arm of NK-cell biology is essential for identifying biomarkers of operational tolerance and for developing novel strategies aimed at achieving long-term graft survival with reduced immunosuppression.

One of the principal mechanisms by which NK cells may promote immune tolerance is the selective elimination of donor-derived APCs, particularly dendritic cells, and activated alloreactive T lymphocytes. By killing donor dendritic cells, NK cells effectively limit direct allorecognition and dampen the initiation and amplification of the adaptive alloimmune response (Yu et al. 2006; Pontrelli et al. 2020).

Additionally, the CD56^{bright} NK-cell subset, which predominates in secondary lymphoid organs and expresses high levels of the inhibitory receptor NKG2A, possesses significant immunoregulatory capacity. These cells can secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor- β , thereby suppressing the proliferation and effector functions of conventional T cells (Pontrelli et al. 2020). Interestingly, in some transplant settings (notably liver transplantation), donor-derived CD56^{bright} NK cells constitute the dominant population infiltrating the graft early after transplantation, suggesting a potential role in local tolerance induction (Moroso et al. 2010).

A particularly important aspect of immune tolerance is the bidirectional crosstalk between NK cells and Tregs. Experimental models have demonstrated that adoptively transferred Tregs can prevent bone marrow rejection by suppressing alloreactive NK cells and modulating the expression of activating receptors on NK cells recognizing donor major histocompatibility complex (MHC) class I molecules (Mahr et al. 2017). Conversely, NK cells can influence Treg homeostasis and function through IFN- γ secretion and direct cell-cell interactions (Zagorulya et al. 2023; Ruan et al. 2024). This mutual regulation helps maintain the balance between effector responses and immune suppression.

Such bidirectional communication between innate and adaptive immune components constitutes an important link in the process of immune adaptation to the transplanted organ.

A critical process determining the functional competence of NK cells toward donor tissues is NK-cell education (also known as licensing). Mature NK cells acquire the ability to respond to cells lacking self-HLA class I molecules through the interaction of inhibitory KIR receptors with their cognate HLA ligands. In the transplant setting, reeducation of NK cells can occur in the presence of donor cells, leading to a gradual reduction in alloreactivity. NK cells that become tolerant to donor antigens display decreased cytotoxic responses and reduced production of pro-inflammatory cytokines.

However, not all NK-cell subsets undergo effective reeducation. Recent studies have shown that the NKG2A⁺KIR⁺ subpopulation exhibits particularly strong alloreactivity that persists after transplantation despite immunosuppression (Ruan et al. 2024). This suggests that while some NK-cell subsets successfully adapt and contribute to immune tolerance, others remain resistant to reeducation and may serve as a source of chronic allograft injury.

Chronic CMV infection, the most common viral complication after kidney transplantation, drives the expansion of adaptive (memory-like) NK cells characterized by the NKG2C⁺CD57⁺ phenotype. These cells acquire features of immunological memory—a unique property within the innate immune system (Schlums et al. 2015). Adaptive NK cells play a crucial role in controlling CMV replication, and their higher frequency prior to transplantation is associated with a reduced incidence of CMV viremia post-transplant (Ataya et al. 2020). In the late post-transplant period, their accumulation primarily reflects long-term immune remodeling directed toward effective antiviral defense (Hassan et al. 2022).

While their contribution to allograft tolerance remains controversial, some evidence suggests that CMV-driven expansion of adaptive NK cells may also promote the development of alloreactive clones capable of mediating chronic graft injury (Alari-Pahissa et al. 2025). Conversely, other studies indicate that these cells may support tolerance by eliminating activated autologous T cells (Bielekova et al. 2006).

The shift observed in the late post-transplant period from a highly cytotoxic phenotype toward a more regulatory and adaptive phenotype may reflect the process of immune adaptation to the transplanted kidney (Ruan et al. 2024). In the early phase after transplantation, highly cytotoxic NK cells predominate, favoring graft injury. Over time, under the influence of chronic donor antigen exposure and immunosuppressive therapy, NK cells undergo gradual reeducation, accompanied by increased expression of inhibitory receptors (NKG2A, T-cell immunoreceptor with Ig and ITIM domains (TIGIT)) and decreased cytotoxic potential (Qin et al. 2023). In conclusion, NK cells exhibit a dual role in kidney transplantation. On the one hand, they act as potent mediators of allograft injury through ADCC, missing-self recognition, and pro-inflammatory cytokine release. On the other hand, they can promote immune tolerance and adaptation by eliminating donor dendritic cells, interacting with Tregs, and undergoing phenotypic reprogramming (Yu et al. 2006; Pontrelli et al. 2020). The processes of NK-cell education, reeducation, and bidirectional crosstalk with adaptive immune components ultimately determine the balance between rejection and tolerance. Identification of NK-cell phenotypes associated with stable graft function may provide valuable biomarkers of immune adaptation and potential targets for therapeutic intervention (Ruan et al. 2024).

8. Conclusions and Future Perspectives

In conclusion, NK cells represent a heterogeneous and highly plastic population that plays a dual role in kidney transplantation. They contribute to allograft injury through ADCC, missing-self recognition via KIR-HLA mismatch, and secretion of cytotoxic mediators such as Ksp37. Simultaneously, they can promote immune tolerance by eliminating donor

dendritic cells, interacting with Tregs, and undergoing phenotypic reprogramming toward regulatory and adaptive subsets. The balance between these opposing functions is shaped by NK-cell education, reeducation, CMV-driven adaptation, and the degree of immunosuppression. Recent high-dimensional studies have significantly advanced our understanding of NK-cell biology in transplantation and highlighted specific subsets as potential biomarkers.

Future research should focus on prospective validation of NK-cell signatures for early prediction of graft dysfunction, development of NK-targeted therapies, integration of NK-cell monitoring into routine post-transplant care, and systematic comparison of circulating vs. tissue-resident NK phenotypes together with the full spectrum of activating NCR, NKG2C/D and inhibitory receptors to refine biomarker panels and therapeutic strategies. Ultimately, a deeper understanding of NK-cell plasticity may pave the way for personalized immunosuppression and improved long-term kidney allograft survival.

9. Limitations

This narrative review has several limitations. Most data come from observational studies and experimental models with relatively small sample sizes. There is significant heterogeneity in immunosuppressive regimens and patient populations across studies, which limits direct comparisons. High-dimensional analyses are still performed in few centers, and prospective validation of NK-cell-based biomarkers is lacking. Finally, the exact contribution of NK cells to operational tolerance in kidney transplantation remains incompletely understood due to the scarcity of tolerant patient cohorts.

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Competing Interest Statement

The authors declare that they have no competing interests.

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Compliance with Ethical Standards

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Author Contributions

Anna Skotny: Conceptualization, literature review, writing—original draft preparation, writing—review and editing; Paweł Poznański: Literature review, writing—original draft preparation; Katarzyna Kościelska-Kasprzak: Literature review, writing—original draft preparation; Dorota Bartoszek: Literature review, writing—original draft preparation; Marcelina Żabińska: Literature review, writing—original draft preparation; Dorota Kamińska: Conceptualization, writing—review and editing, supervision; Magdalena Krajewska: writing—review and editing, supervision.

All authors contributed to the interpretation of the literature, critically revised the manuscript for important intellectual content, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Use of Artificial Intelligence

AI-assisted tools were used solely for technical support in preparing a conceptual figure, strictly based on detailed instructions provided by the authors. No AI tools were used to generate scientific content, interpret data, or formulate conclusions.

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