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Review

Immunogenetic Harmony and Discord: The Expanding Role of Killer Cell Immunoglobulin-like Receptors (KIR) in Hematopoietic Stem Cell Transplantation (HSCT) Outcomes

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Abstract

Killer cell immunoglobulin-like receptors (KIRs) that regulate the activity of the natural killer (NK) cells are determinants of immune response during hematopoietic stem cell transplantation (HSCT). They interact with, and thus modulate alloreactivity, graft success, and post-transplant immune surveillance with human leukocyte antigen (HLA) class I molecules. Recently, an increased interest has been generated in exploiting KIR-HLA interactions to enhance the success of transplantation. It has given us an opportunity for a critical, in-depth review of the KIRs' biological functionality, the diversity, and clinical significance in HSCT among various populations across the world. This review evaluates the outcomes of graft-versus-host disease (GVHD), relapse, risk of infections, and survival with respect to KIR genotype matching, ligand recognition, and licensing. Evidence suggests that donor KIR B haplotypes and KIR-ligand mismatching can optimize graft-versus-leukemia (GVL) effects without increasing GVHD in certain HSCT settings. In the future, integration of KIR-HLA mismatching for donor selection will be essential for achieving the best results for HSCT.

Keywords

KIR-HLA interactions, natural killer cell licensing, hematopoietic stem cell transplantation, graft-versus-host disease, bioinformatics, CAR-NK therapy

Article History

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1. Introduction

Hematopoietic stem cell transplantation (HSCT) is an important element in the management of hematologic malignancies, bone marrow failure diseases, and some instances, immunodeficiencies. The therapy involves the substitution of unhealthy/insufficient hematopoietic progenitors with healthy stem cells of the donor, with the aim of reconstituting the recipient with a hematopoietic and immune system. Problems like graft-versus-host disease (GVHD), infection, and disease relapse currently plague long-term results despite the clinical success of HSCT [1]. A significant role is played by killer cell immunoglobulin-like receptors (KIRs) on the surface of natural killer (NK) cells. KIRs recognize particular human leukocyte antigen (HLA) class I molecules and modulate the effects on NK cell cytolytic activity, which affect graft acceptance, tolerance, and alloreactivity. Beneficial graft-versus-leukemia (GVL) and harmful GVHD have been associated with KIR-HLA mismatches between the donor and the recipient [2]. This review aims to explore this multidimensional liaison of KIRs in HSCT and to synthesize recent knowledge on their population genetics, ligand recognition, regulatory functions, and translation strategies in the optimal use of transplantation processes.

After revealing the clinical significance of KIR-HLA interactions in HSCT, it is critical to investigate how these receptors differ across global populations, as population-level genetic diversity provides the foundation for understanding donor compatibility and transplant outcomes.

2. Global KIR Gene Distribution and Evolutionary Insights

KIR gene family, which is within chromosome 19q13.4, leukocyte receptors complex, is variably composed of genes and contains alleles, differing in content and across many populations across the globe. KIR haplotypes are typically divided into two groups, A and B: haplotype A also includes mostly inhibitory KIRs whereas haplotype B contains both inhibitory and activating KIRs [3]. These haplotype distributions are affected by evolutionary forces such as the prevalence of pathogens, reproductive success, and local adaptation by geography. An example is that activation of KIRs such as KIR2DS1 and KIR3DS1 is over-represented in Africans and East Asians, as depicted in Table 1, where pathogens that are responsible for high rates of infection in those populations have caused the evolution of NK cells to greater responsiveness through adaptive selection. On the other hand, repressive KIRs such as the KIR2DL1 and KIR2DL3 occur more in the European and Middle Eastern population [4]. It has been shown that KIR and HLA class I genes have been co-evolving where there are balanced immune tolerance with cytotoxic readiness. It is vital to determine these KIR patterns that are population-specific in terms of outcomes in HSCT and the personalization of the donor selection of ethnically diverse populations [5].

Table 1. Comparative KIR gene frequencies in select world populations.

KIR Gene	African (%)	East Asian (%)	South Asian (%)	European (%)	Middle Eastern (%)	Reference
KIR2DL1	88	91	87	93	90	[6]
KIR2DS1	52	24	41	33	45	[6]
KIR3DL1	95	85	89	92	90	[7]
KIR3DS1	60	28	39	30	48	[8]

Although population genetics offers light on the patterns of distribution and evolutionary forces influencing KIR variety, a more thorough analysis of the molecular processes controlling KIR-HLA binding and NK cell activation is necessary to comprehend their clinical significance.

3. Molecular Mechanisms of KIR-HLA Binding

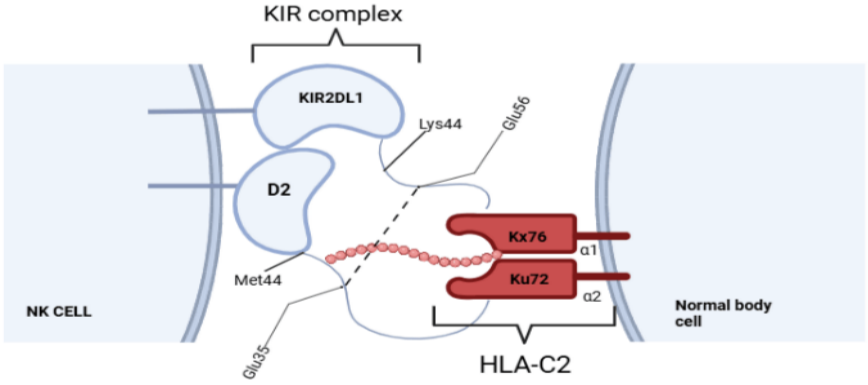

Figure 1. Structural model of KIR2DL1 binding to HLA-C2 with antigenic peptide, highlighting key interaction sites, such as Lys44 and Glu56 on KIR2DL1, interacts with residues like Met44, Ku72, and Kx76 on HLA-C2.

The outcome of KIR signaling is dependent on the outcome whether it interacts with the HLA class I ligands. Inhibitory KIRs often have immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic tails and target certain HLA epitopes to prevent NK cell activation. Activating KIRs interact with adaptor molecules such as DAP12, which include immunoreceptor tyrosine-based activation motifs (ITAMs), sending stimulatory signals upon ligand interaction, as depicted in Figure 1 [9].

Specific KIR-HLA binding pairs include: KIR2DL1-HLA-C2, KIR2DL2/3-HLA-C1 and KIR3DL1-HLA-Bw4.

These connections control NK cell education (licensing), cytotoxicity, and cytokine production. Crucially, KIR-HLA mismatches in which the donor's NK cells lack inhibitory signals due to the absence of cognate HLA ligands in the recipient can result in NK cell alloreactivity as shown in Table 2. This has been linked to lower recurrence rates in acute myeloid leukemia (AML) and improved GVL effects. Recent crystallographic investigations have revealed structural details about the conformational dynamics of KIR-HLA-peptide complexes, suggesting that the attached peptide also influences KIR recognition. This peptide requirement adds another layer of intricacy and may affect NK cell responsiveness during infections or tumor transformation [10].

Table 2. Summary of KIR-HLA ligand interactions and functional outcomes.

KIR Receptor	Cognate HLA Ligand	Signal Type	Functional Role	Clinical Implication	Reference
KIR2DL1	HLA-C2	Inhibitory	NK inhibition, self-tolerance	GVL effect when mismatched	[11]
KIR2DL3	HLA-C1	Inhibitory	NK tolerance	Cytomegalovirus (CMV) control, relapse modulation	[11]
KIR2DS1	HLA-C2 (low affinity)	Activating	Pro-inflammatory signaling	GVHD risk in certain settings	[12]
KIR3DL1	HLA-Bw4	Inhibitory	Controls NK cytotoxicity	Relapse protection	[12]

These basic insights serve as the foundation for assessing how KIR-HLA interactions impact a variety of clinical settings. Building on this molecular understanding, the following part investigates the role of KIRs in non-malignant HSCT, which focusses on immune reconstitution rather than tumor management.

4. KIRs in Non-Malignant HSCT Indications

The function of KIR-HLA interactions in HSCT has mostly been studied in the context of hematological cancers, where the GVL effect is critical. However, an increasing body of data supports the role of KIRs in non-malignant illnesses undergoing HSCT, such as severe aplastic anemia, primary immunodeficiencies, thalassemia major, sickle cell disease (SCD), and some hereditary metabolic abnormalities. The Function of KIR-HLA Mismatching in Balancing GVL and GVHD KIR-HLA mismatching occurs when donor NK cells express inhibitory KIRs, while the recipient lacks the associated HLA ligands. This absence eliminates NK inhibitory signals, resulting in increased NK alloreactivity. In malignant HSCT, this enhances GVL activity by allowing NK cells to eliminate leukemic blasts and remaining host haematopoietic cells. NK cells minimize the likelihood of GVHD by removing host antigen-presenting cells, which are necessary for T-cell activation. Thus, KIR-HLA mismatch improves anti-leukemic actions without worsening GVHD. In non-malignant HSCT, where GVL is not the primary goal, this process is nonetheless essential since NK-mediated clearance of host immune cells can minimize graft rejection and promote sustained engraftment while lowering the risk of GVHD [13].

The major treatment objective in these situations is not tumor eradication, but rather long-term engraftment, immunological reconstitution, and reduction of GVHD. NK cells, particularly those with KIR-mediated recognition systems, play an important role in enhancing graft acceptance and early immune control in non-malignant HSCT. Certain KIR-HLA mismatches, which are often considered detrimental in cancer due to increased GVHD risk, may provide benefits in non-malignant settings by improving NK cell-mediated clearance of residual recipient hematopoietic cells, reducing graft failure without inducing excessive alloreactivity [14].

KIR-HLA interactions play a role in reducing graft rejection on a cellular level. Before transplantation, the host NK-cells are educated during development, the host NK-KIRs identify self-HLA class 1 molecules and create an inhibitory signal preventing attack as shown in Figure 2. After transplantation, the newly acquired NK-cells are not educated towards host cells contain KIRs that interact with host cells containing HLA molecules that interact with donor KIRs and an activating signal is produced leading to clearance of host APCs and host NK cells. This leads to dampened T-cell priming, as APCs are killed host T-cells may not be activated reducing the chances GVHD. Attack on the host NK-cells further reduces the risk for GVHD.

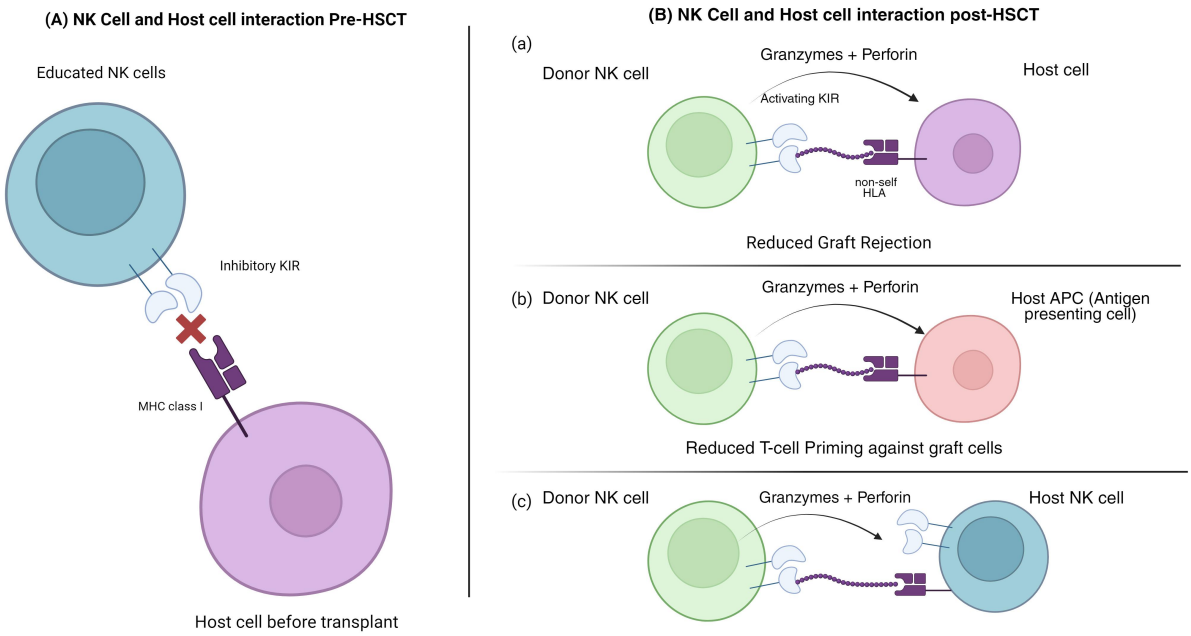

Figure 2. Mechanisms of NK cell activation and inhibition mediated by KIR-HLA interactions in HSCT.

Recent clinical findings indicate that donor KIR haplotype B, particularly those including activating KIRs such as KIR2DS1 or KIR3DS1, may be linked with enhanced engraftment and a lower risk of chronic GVHD in non-malignant HSCT. Studies on thalassemia and SCD patients receiving matched unrelated donor transplantation have also found links between inhibitory KIR-HLA combinations and positive outcomes, such as improved hematological recovery and fewer opportunistic infections [15].

In initial immunodeficiencies, when fast immune reconstitution is critical for infection control, KIR-HLA interactions serve two functions as shown in Figure 2. First, they affect the speed and strength of NK cell maturation and licensing after transplantation. Second, they influence early NK cell cytotoxicity, which affects viral clearance and host-pathogen defense during the critical post-conditioning period. Furthermore, emerging data suggest that KIR-driven NK cell tolerance mechanisms can help to reduce immune-mediated damage to healthy tissues in non-malignant HSCT recipients, particularly in cases where autoimmunity or inflammatory dysregulation underpins disease pathophysiology (e.g., HLH or autoimmune cytopenia) [16].

Although KIR-HLA dynamics have a significant impact on transplant outcomes, NK cell behaviour is regulated by a larger network of immunological receptors. As a result, the section that follows focuses on KIRs' integrative involvement with other NK and immunological checkpoint receptors in modulating NK functionality after HSCT.

5. Integrative Role of KIR with Other Immune Receptors

Despite these promising outcomes, different institutions continue to use different routine KIR typing procedures in non-malignant transplant programs. The validation of KIR-based risk classification in these groups and the direction of clinical application depends on larger multi-center prospective research and databases. NK cell responses are regulated by KIRs, which are essential but not isolated elements. Through co-expression and interaction with many different immune receptor families, their activity is dynamically controlled. NK cell maturation, licensing, effector function, and homeostasis are determined by the balance and synergy between KIRs and other NK and immune checkpoint receptors. This is especially important in the context of HSCT, where tolerance and immune reconstitution are crucial [17].

5.1 NKG2A/CD94 Receptor Complex

The heterodimeric, inhibitory complex known as the NKG2A/CD94 binds to HLA-E presenting leader peptides derived from classical HLA class I molecules, a non-classical MHC class I molecule that presents peptides primarily derived from the leader sequences of other HLA class I proteins. In early-stage NK cells and $CD8^+$ T cells, NKG2A expression is particularly prominent. It also serves as a compensatory inhibitory mechanism when KIR expression is absent or delayed after transplantation [18].

5.1.1. Functional Relevance in HSCT

During the early post-transplant period, while KIR expression is still developing, NKG2A controls the NK cells' inhibitory checkpoint. HLA-E polymorphisms affect the binding affinity of NKG2A, which in turn affects NK inhibition (e.g., HLA-E*01:01 vs. *01:03). In clinical studies, therapeutic inhibition of NKG2A (e.g., monalizumab) is

being studied to improve NK-mediated anti-leukemic benefits without raising the risk of GVHD [18]. NKG2A expression dominance during early NK reconstitution may transiently suppress GVL, but its later downregulation restores cytotoxic balance.

5.2 Fcγ Receptors and Antibody-Dependent Cellular Cytotoxicity

The primary Fc receptor on NK cells, FcγRIIIa mediates antibody-dependent cellular cytotoxicity (ADCC) through binding to the Fc portion of IgG antibodies. Strong CD16 expression and function are necessary for the post-transplant efficacy of monoclonal antibody-based treatments (such as trastuzumab and rituximab) [19].

5.2.1 Key Considerations

Polymorphisms that impact affinity for IgG1 and IgG3 subclasses include FcγRIIIa-V158F. The interactions between KIR and CD16 work in concert. For instance, NK cells that co-express high-affinity CD16 and activating KIRs (such as KIR2DS1) have increased cytotoxic responses. In NK cell infusions, cytokine preactivation (e.g., with IL-15 or IL-2) can increase CD16 and enhance ADCC capability [19]. Relapse after HSCT can be potentially reduced by a strong CD16 function due to cytokine enhanced expression amplification of NK ADCC.

5.3 Natural Cytotoxicity Receptors: NKp30, NKp44, and NKp46

The activating receptors known as natural cytotoxicity receptors (NCRs) can detect a wide variety of ligands, including those that are expressed by cells that are under stress, infected, or transformed. NCRs are essential for direct NK cell-mediated lysis and are not MHC-restricted, unlike KIRs.

5.3.1 Clinical Implications in HSCT

Incompletely licensed NK cells may compensate through increased NCR-mediated cytotoxicity and NK cell cytotoxicity during the early post-transplant period. Downregulation of NCRs after HSCT has been linked to delayed immune reconstitution and susceptibility to viral infections, such as CMV reactivation. Pharmacologic or *ex vivo* cytokine modulation (e.g., IL-21, IL-18) can improve NCR function and increase cytotoxicity [20]. Early downregulation immediately after HSCT and later cytokine mediated enhancement of the receptors can achieve increased graft acceptance and antiviral and anti-leukemic function.

5.4 LILRB1 (ILT2/CD85j): A Broad Inhibitory Checkpoint

LILRB1 is an inhibitory receptor found on NK, T, and myeloid cells that binds to a wide range of classical and non-classical MHC class I molecules, including HLA-G, HLA-F, and certain HLA-A/B variants [21].

5.4.1 Role in Transplantation

LILRB1 can inhibit NK cell responses in the presence of sufficient HLA expression, potentially overriding activating KIR signals. In the maternal-fetal interface, LILRB1 helps maintain immune tolerance, suggesting potential parallels in HSCT tolerance mechanisms. Its overexpression in some transplant settings may be associated with immunosuppression and viral persistence [21]. Overexpression may lead to reduced GVL effect but its normal engagement is associated with dampened NK cell and T cell activity enhancing post-HSCT immune tolerance. A balance must be found.

5.5 TIGIT, TIM-3, and Other Emerging Immune Checkpoints

Multiple inhibitory and co-stimulatory receptors have been found on NK-cells.The most extensively studied among these are TIGIT (T cell immunoreceptor with Ig and ITIM domains), which competes with DNAM-1 for binding to CD155 and reduces NK-cells ability to kill target cells. Secondly, TIM-3 which binds to galectin-9 and phosphatidylserine and contributes to NK cell exhaustion. Lastly, PD-1 (programmed death-1), which's expression on NK cells post-HSCT correlates with impaired function, particularly in relapsed malignancies [22].

5.5.1 Clinical Prospects

Dual checkpoint blockade strategies combining KIR inhibition with TIGIT or PD-1 blockade are being evaluated to overcome NK cell dysfunction in relapsed HSCT recipients. Understanding the co-expression dynamics of these receptors is essential for designing effective adoptive NK cell therapies [23]. Post-HSCT sustained expression of all three receptors leads to a negative impact on GVL and increased disease relapse.

5.6 Integration of NK Receptor Families in Post-Transplant Immune Reconstitution

NK receptors and their interactions can be understood through the stages of NK cell development after transplant. In the early stages, NK cells are immature and NKG2A is the main receptor that controls NK activity; KIRs and NCRs are absent. NK cells are less aggressive but safer, leading to a reduced risk of damaging the graft. In the later phase KIRs,

NCRs and CD16 take over the regulation of NK attack towards viruses, cancer cells and antibody-coated targets, respectively. This leads to stronger anti-leukemia activity and ADCC. By manipulating these receptors simultaneously externally using cytokines or monoclonal antibodies, optimized clinical treatments can be devised. Following HSCT, NK receptor expression occurs on a specific time scale. Immature NK cells appear within the first 2-4 weeks and mostly express NKG2A, with little KIR or NCR expression. Inhibitory KIRs begin to reactivate between 1-3 months, followed by activating receptors including NKp30, NKp46, and CD16, between 3-6 months. The full maturation of the NK receptor repertoire may take 6-12 months, depending on clinical circumstances [24].

Understanding how KIR expression is regulated is crucial, given the complex receptor interaction that controls NK cell development and function. The epigenetic processes that influence KIR variety during NK cell growth and post-transplant reconstitution are next discussed.

6. Epigenetics of KIR Expression

The expression of KIRs on NK cells is influenced by the presence of KIR genes but also by a complex network of epigenetic regulation that determines gene accessibility, transcriptional activity, and cellular heterogeneity. Epigenetic mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs play a crucial role in establishing the stochastic and diverse expression of KIR among NK cell subsets, as shown in Figure 3. This modulation of KIR gene expression is particularly relevant in the context of HSCT, where immune reconstitution, tolerance, and antitumor surveillance heavily depend on the functional maturity of NK cells [25].

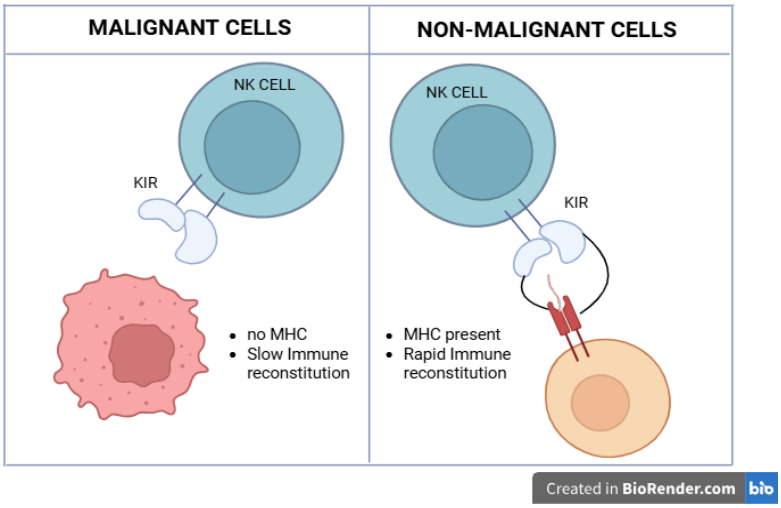

Figure 3. Comparison of KIR-HLA functional interactions in malignant vs non-malignant HSCT settings. Illustrated are differential NK cell roles, immune reconstitution kinetics, and clinical implications.

KIR genes are located within the leukocyte receptor complex on chromosome 19q13.4. Although they are inherited in a Mendelian manner, their transcription is independently regulated within individual NK cells. This leads to each NK cell expressing a unique combination of inhibitory and activating KIRs, which creates a diverse and adaptable NK cell population. Epigenetic silencing of KIR promoters through DNA hypermethylation blocks transcription initiation, while demethylation allows for gene activation. Bisulfite studies have also verified that the DNA methylation status of KIR promoters is significantly associated with cell surface expression patterns of KIRs [26].

Other issues associated with histone changes are the accessibility of KIR genes. Dynamically open chromatin signatures such as H3K4me3 and H3K9ac become more frequent at promoters of expressed KIR genes, whereas repressive scenarios have been associated with H3K27me3 or H3K9me3. These histone modifications are regulated dynamically through the development of NK cell and, therefore, can be affected by external signals, such as exposure to cytokines or the surrounding stress. It is interesting to notice that the epigenetic landscape of NK cells can be very different in the cases of transplantation when cells are either of autologous or allogenic progenitors [27]. Non-coding RNAs, particularly microRNAs (miRNAs), have been identified in recent works as the KIR expression fine-tuners, after transcription. In particular, miR-146a and miR-181a have been described to act as regulators by targeting elements of the signaling pathways critical in the context of KIR activation and stability. Inadequate regulation of these miRNAs after HSCT might be one factor in impaired or delayed NK cell maturation, which may result in poor immune responses against recurrence or infection [28].

Epigenetic factors that also play a role in the situation of HSCT are the immunosuppressive drugs, the conditioning regimen, and viral reactivation on the chromatin of NK cells. Other agents employed in the treatment of relapse or conditioning before transplant, such as decitabine and azacytidine, have global effects on hypomethylation and can accidentally alter the pattern of KIR expression, as illustrated in Figure 3. The main epigenetic regulators that influence

KIR expression and their functional significance in HSCT are summarized in Table 3. Chronic CMV infection after transplant has also been linked to the growth of $NKG2C^+$ NK cells with modified KIR repertoires, indicating that epigenetic reprogramming in response to antigenic challenge may influence NK cell function in a long-term way. CMV reactivation is a key immunological factor driving NK cell remodeling after HSCT. CMV triggers the expansion of adaptive or "memory-like" NK cell subsets, including $NKG2C^+CD57^+$ cells with distinct epigenetic markers. These CMV-induced NK cells show lasting reductions in inhibitory receptors like NKG2A, while selectively increasing certain KIRs, such as KIR2DL2/3 and KIR2DL1, resulting in a more mature and functionally effective NK cell repertoire. This reorganization enhances antiviral defense and may boost GVL activity, but it can also influence immunological recovery times and vulnerability to opportunistic infections. Therefore, CMV-driven NK education plays an important role post-transplant, continuously shaping KIR diversity, NK licensing strength, and long-term immune competence [28].

Technological developments like single-cell RNA-seq and single-cell ATAC-seq (assay for transposase-accessible chromatin) are starting to clarify the transcriptional and epigenetic diversity of NK cell subsets after HSCT. These instruments provide fresh perspectives on the ways in which KIR expression patterns are influenced by donor-, disease-, and treatment-specific variables. The development of innovative therapies targeted at improving NK cell effectiveness in the post-transplant setting requires an understanding of the epigenetic architecture governing KIR expression. The use of epigenetic modifiers to restore equilibrium in situations of KIR silencing or to selectively upregulate activating KIRs is a therapeutic approach that is currently being investigated. However, these initiatives need to be handled carefully since extensive epigenetic regulator alteration might result in unanticipated immunological dysregulation [29].

Table 3. Epigenetic regulators of KIR expression and their functional implications in HSCT.

Epigenetic Mechanism	Example	Effect on KIR Expression	Clinical Relevance in HSCT	Reference
DNA Methylation	CpG hypermethylation	Silencing of KIR promoters	Alters NK cell licensing, delays reconstitution	[27]
Histone Modification	H3K4me3, H3K27me3	Chromatin opening or condensation	Influences transcriptional accessibility	[27]
Non-coding RNAs	miR-146a, miR-181a	Post-transcriptional suppression	Modulates KIR expression dynamics post-HSCT	[30]
Hypomethylating Agents	Azacytidine, Decitabine	Global demethylation	May enhance or disrupt KIR gene expression	[31]
Viral Infection	CMV	Expansion of adaptive NK subsets	Epigenetic reprogramming of NK cell memory	[31]

The following section highlights how bioinformatics and predictive modelling are increasingly being used to improve donor selection and stratify HSCT risk.

7. Bioinformatics and Predictive Modeling

Clinical decision-making for HSCT has to incorporate bioinformatics and computer modelling due to the explosion of immunogenetic data produced by high-throughput sequencing technology. With their wide range of polymorphism, gene copy number variation, and fluctuating expression, the intricacy of KIR and HLA interactions poses a significant obstacle to immunological risk assessment, donor selection, and result prediction. KIR-HLA immunogenetic profiles can now be examined in greater detail to optimize and tailor HSCT processes due to advances in modern computational methods, such as machine learning (ML), artificial intelligence (AI), and advanced algorithm-based applications, as described in Table 4 [32]. Among the post-transplant complications that it is possible to predict with some platforms integrating donor-recipient immunogenetic data are GVHD relapse, viral reactivation and overall survival. One such algorithm is the Predicted Indirectly Recognizable HLA Epitopes (PIRCHE) algorithm, which takes into consideration the number of mismatched HLA-derived peptides that the antigen-presenting cells of the recipient might be able to serve up indirectly. Although PIRCHE was originally designed with HLA matching, the predictive power has been extended to incorporate KIR genotypes into models that give an estimate of the risk of immunological modulation and NK cell alloreactivity [33].

HLA Matchmaker is another familiar approach that studies HLA matching on the epitope level and can match HLA better than traditional antigen-based analysis. HLA Matchmaker offers a deeper immunological compatibility index when combined with KIR genotyping, indicating donor-recipient combinations that are expected to enhance GVL effects or reduce alloreactivity. A specialized bioinformatics tool called KIR-HLA Matcher was created to evaluate how well donors' KIR genes match recipients' matching HLA ligands. This platform can classify transplant pairs according to the probability of either positive or negative NK cell responses by calculating inhibitory and activating KIR-ligand interactions. Weighted grading methods based on clinical outcome data from transplant registries and population-specific allele frequencies are incorporated into recent versions of this instrument [34]. A growing number of HSCT outcome prediction models are being constructed using machine learning methods. KIR genotype, HLA typing, disease state, conditioning regimen, CMV status, donor age, and graft source are some of the factors that these models

frequently use in order to forecast outcomes like relapse risk, GVHD incidence, and survival probability. Techniques for supervised learning, such support vector machines and random forests, have demonstrated promise in creating reliable outcome classifiers. Unsupervised clustering techniques are also employed to find new subgroups of NK cells with unique immunogenetic characteristics [35].

Applications of artificial intelligence in single-cell data processing are also growing. Large-scale datasets recording NK cell transcriptomes and surface phenotypes are being mined to find predictive biomarkers and functional signatures since the development of single-cell RNA sequencing and mass cytometry (CyTOF). These databases enable real-time correlations between clinical events and KIR expression fluctuation and functioning [36]. To increase the precision of donor-recipient matching, bioinformatics pipelines are being included in donor registries regularly. The DKMS donor registry, for instance, has begun assessing KIR compatibility using automated techniques in addition to conventional HLA typing. In addition to making the donor selection process easier, these cutting-edge techniques provide real-time risk classification and enable customized modifications to immunosuppressive treatments or conditioning regimens [37]. In the future, integration of multi-omics data such as genomics, transcriptomics, proteomics, and epigenomics into AI-powered platforms will enable comprehensive modeling of transplant immunobiology. These systems-level strategies are expected to transform personalized transplantation, allowing clinicians to customize donor selection, graft modification, and post-transplant management based on each patient's unique immunogenetic profile. Although several bioinformatics platforms and AI-based models have been developed for HSCT, their clinical usefulness remains limited due to inconsistent validation, lack of standardization, and variable performance across populations. Tools like PIRCHE, HLA Matchmaker, and KIR-HLA Matcher offer more detailed immunogenetic insights; however, they often depend on diverse scoring systems and incomplete allele coverage, reducing their practicality for routine donor selection. Similarly, machine learning models often suffer from overfitting, limited external validation, and unclear interpretability, while single-cell and multi-omics techniques remain costly and not broadly scalable in clinical settings. Consequently, despite their promise, these computational approaches will need more rigorous benchmarking and prospective testing before they can be fully integrated into evidence-based HSCT decision-making [38].

Table 4. Key bioinformatics tools and models in KIR-HLA guided HSCT decision-making.

Tool/Algorithm	Primary Function	Integration with KIR Data	Clinical Application	Reference
PIRCHE	Predicts HLA-derived indirect epitopes	Under development	GVHD and relapse risk prediction	[39]
HLA-Matchmaker	Epitope-level HLA matching	Used in combined analysis	Refined donor selection	[40]
KIR-HLA Matcher	Scores KIR-HLA interactions	Central tool	NK cell compatibility assessment	[40]
Machine Learning Models	Predictive modeling of outcomes	High-level integration	Personalized risk stratification	[41]
Single-cell AI Pipelines	NK subset discovery and function mapping	In research phase	Biomarker identification for relapse or GVHD	[42]
Multi-Omics Integrators	Systems-level transplant modeling	Future development	Comprehensive donor-recipient matching framework	[43]

As computational platforms rely largely on precise and high-resolution immunogenetic input, their usefulness is directly proportional to the accuracy of KIR typing. The following section discusses developing technologies that provide precise KIR genotyping for research and clinical usage.

8. KIR Typing Technologies

The accurate typing of KIR genes has become increasingly important in HSCT for guiding donor selection, risk stratification, and immune compatibility evaluation as described in Table 5. The KIR locus is notably complex, characterized by variable gene content, extensive allelic diversity, and highly homologous sequences, which pose significant technical challenges for genotyping. However, recent advancements in molecular and sequencing technologies have greatly enhanced the accuracy, speed, and scalability of KIR typing, facilitating its broader incorporation into clinical and research workflows [44].

KIR genes are located in highly similar tandem arrays on chromosome 19q13.4 of the leukocyte receptor complex. Significant variation may be seen in this genomic region's allele sequences and gene content, which refers to the existence or lack of certain KIR genes. Generally speaking, KIR haplotypes are categorized as either A or B, with haplotype B having a greater amount of activating genes and haplotype A mostly consisting of inhibitory genes. As a result, thorough KIR genotyping has to take into consideration structural rearrangements, allelic variation, and copy number variations in addition to gene presence or absence [45].

Table 5. Summary of KIR typing technologies and their applications in HSCT.

Method	Resolution	Detectable Features	Advantages	Limitations	Clinical Use	Reference
PCR-SSP	Low	Gene presence/absence	Fast, cost-effective	No allele-level data	Routine screening	[46]
PCR-SSO	Intermediate	Limited allele discrimination	Higher specificity than SSP	Limited by probe design	Clinical research	[46]
qPCR	Intermediate	Copy number variation	Quantitative, easy to interpret	Cannot resolve alleles	Copy number variation (CNV) assessment	[47]
NGS (short-read)	High	Gene content + allele typing	High-throughput, multiplexable	Requires specialized software	High-resolution genotyping	[48]
Long-read Sequencing	Very High	Full haplotypes, structural variants	Resolves complex KIR regions	High cost, technical complexity	Research, rare variant detection	[49]
aCGH/ddPCR	Intermediate	CNVs, deletions, duplications	Rapid and sensitive CNV			[50]

8.1 Polymerase Chain Reaction-Based Methods

Traditional KIR typing has included a significant portion of its procedure with the polymerase chain reaction with sequence-specific primer (PCR-SSP). The method makes it possible to reveal the existence or lack of specificity of certain KIR genes and is quite fast and cost-efficient. Nonetheless, PCR-SSP has limited requirement to differentiate the allelic variants and is subjected to the possibility of having false negative results or cross-reactivity because of the high homology between KIR genes. To improve specificity, PCR is combined with sequence-specific oligonucleotide probes (PCR-SSO), wherein the amplified DNA is hybridized against allele-specific probes which are immobilized onto a membrane or microbeads. Although clinical laboratories now often employ commercial kits utilizing PCR-SSO platforms, resolution is still restricted to low- or intermediate-resolution genotyping [51]. KIR gene CNV is also determined using real-time quantitative PCR (qPCR). This is especially important in transplant environments because NK cell reactivity may be affected by the gene dosage of activating or inhibitory KIRs [51].

8.2 High-Resolution Typing via Next-Generation Sequencing

Through next-generation sequencing (NGS) technologies that are capable of providing high-resolution, allele-level KIR and HLA loci genotyping, the immunogenetics field has experienced a revolution. The same ACP sample can be used to differentiate gene content, CNV, and allelic polymorphisms using NGS-based KIR typing. Whole-gene sequencing enables the differentiation of very similar alleles that differ in only a few nucleotides because it may capture entire copies of KIR transcripts or genomic regions. KIR NGS applies two major strategies, which include amplicon-based targeted sequencing and hybrid capture. Although amplicon-based strategies are more comprehensive and time-saving, hybrid capture offers increased coverage of intronic and regulatory regions possibly influencing the expression of a gene [52]. A number of bioinformatics pipelines have been developed to tackle the specific analysis problems of KIR sequencing e.g., the KIR Typing Pipeline (KIR-Typer), Pushing Immunogenomics to the Next Generation, and KIR-IMP. Such tools compare sequencing reads with curated databases of reference sequences to provide gene calls and an estimated impact of individual genotypes [52].

8.3 Long-Read Sequencing Technologies

Our sequencing systems, e.g. Pacific Biosciences (PacBio) and Oxford Nanopore Technologies platforms, are third generation and enable KIR allele and haplotype direct phasing via long-read sequencing. Such advanced methods are especially effective in resolving structural variations, duplication within segments, and hybrid KIR genes that SK sequencing techniques (NGS) often miss. Researchers were able to find new, previously undocumented, KIR splice variants and isoforms using PacBio full-length cDNA sequencing that have distinct signaling capacities. Because long-read sequencing affords read-through transcripts, it offers a more accurate reconstruction of haplotype structures and more comprehensive functional annotation of KIR variation, as shown in Figure 4 [53].

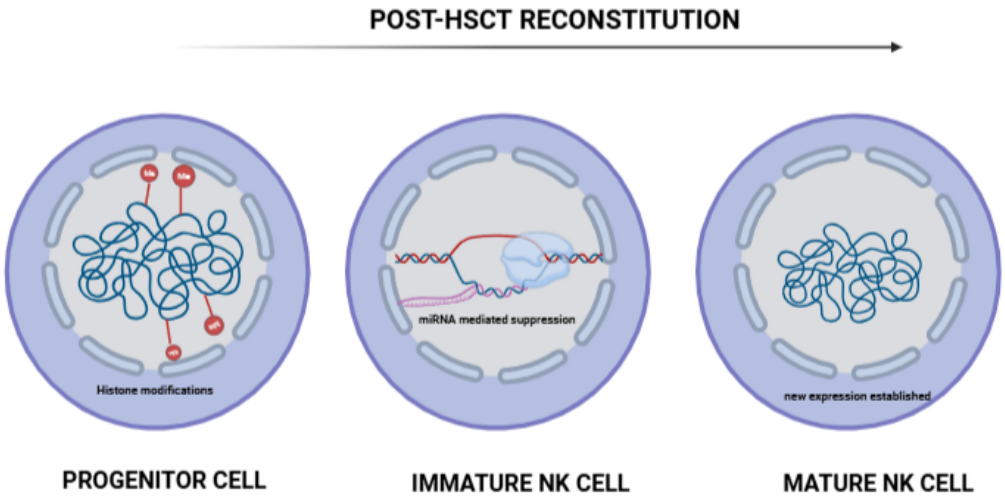

Figure 4. Illustration of epigenetic mechanisms regulating KIR expression. Depicted are promoter methylation, histone modifications, and miRNA-mediated suppression across different stages of NK cell development and post-HSCT reconstitution.

8.4 Genomic Copy Number and Structural Variation Detection

Along with sequencing, array-based techniques, such as array-based comparative genomic hybridization (aCGH) and digital droplet PCR (ddPCR) are used to quantify the copy number of KIR genes to find structural rearrangements. Such techniques deliver sensitive and fast CNV profiling, so they can be incorporated in clinical workflows, especially in assessing activating KIR-rich B haplotypes, in donor selection [54].

8.5 Challenges and Limitations

Despite all the technological advancements, the inability to provide standardization of KIR type poses a constraint of implementing KIR type in clinical contexts. The inconsistencies of typed procedure, reference database, and nomenclature do not allow comparison of results between laboratories and valid meta-analyses. Even more, NGS-based systems seem prohibitively expensive and technologically demanding to replace low-and middle-income countries. Furthermore, clinical recommendations for incorporating KIR genotyping into donor selection processes are still being developed. More prospective multicenter studies are needed to demonstrate the predictive efficacy of certain KIR-HLA combinations and to create clear, actionable criteria for KIR-based matching [55].

8.6 Future Directions

Future developments are likely to include the growth of allele repositories such as the IPD-KIR database, the creation of enhanced machine learning methods for interpreting sequencing data, and the inclusion of KIR information into HLA-matching registries. Furthermore, point-of-care and lab-on-chip genotyping methods are being developed to provide access to accurate KIR typing in a broader range of healthcare settings [56].

High-resolution typing not only improves compatibility assessment, but it also fosters an increased interest in KIR-related pharmacogenomics. The following section investigates how KIR variation affects medication metabolism and therapeutic responses in HSCT patients.

9. Pharmacogenomics and KIR

The merging of pharmacogenomics and KIR genotyping is a growing therapeutic topic in HSCT. KIR-HLA interactions control NK cell activity, which can have a substantial impact on medication metabolism, therapeutic effectiveness, and toxicity, particularly with immunosuppressants, antiviral medicines, and monoclonal antibody therapies. KIR polymorphisms and haplotypic diversity are emerging as effective genetic indicators for predicting individual responses to different pharmacological treatments, as depicted in Table 6. For example, studies have connected particular KIR alleles, such as KIR2DL2 and KIR2DL3, to changes in cyclosporine A pharmacodynamics. Patients with activating KIR-rich B haplotypes may have higher susceptibility to immunosuppressive medication due to increased NK cell activation, necessitating cautious dose adjustments. Similarly, patients with certain KIR-HLA mismatches may experience increased inflammatory responses while using calcineurin inhibitors, increasing the risk of nephrotoxicity or endothelial harm [57]. Furthermore, KIR genotypes can influence the therapeutic efficacy of rituximab and other monoclonal antibodies that rely on ADCC. NK cells expressing FcγRIIIa (CD16) with certain KIR profiles have varying amounts of ADCC activity, which might impact the treatment of residual illness and lymphoproliferative diseases after transplantation. The role of pharmacogenomic studies indicates that individual KIR-HLA combinations change the risk of viral reactivation, especially to CMV, which in turn can influence viral therapies. Variable induction and clearance rates of CMV infection after transplantation with donor-recipient killer-indicator mismatches have been

associated with clinical decision-making regarding potency and duration of antiviral post-transplant prophylaxis. While still in its early stages, the discipline is fast advancing, with ongoing pharmacogenomic experiments expected to yield practical, therapeutically applicable findings. Incorporating KIR genotyping into regular pharmacological monitoring has the potential to increase treatment accuracy, decrease side effects, and improve overall transplant results [58].

Table 6. KIR genotype-linked pharmacogenomic interactions in HSCT.

Drug/Class	KIR Influence	Clinical Impact	Implications for Management	Reference
Cyclosporine A	KIR2DL2 polymorphisms	Altered metabolism, toxicity risk	Dose modulation based on KIR status	[59]
Tacrolimus	Activating KIRs (e.g., KIR2DS1)	Enhanced immune reactivity	Adjusted immunosuppressive regimen	[59]
Rituximab	KIR3DL1 + FcγRIIIa variants	Variable ADCC efficacy	Personalized monoclonal antibody use	[60]
Ganciclovir/Valganciclovir	KIR-HLA mismatch	CMV reactivation risk	Tailored antiviral prophylaxis	[61]

Understanding pharmacogenomic interactions highlights the larger therapeutic potential of NK cell modification. This serves as a logical bridge to the following part, which focuses on new synthetic biology technologies such as CAR-NK cells and KIR-based engineering.

10. CAR-NK and Synthetic Biology Innovations

Recent advances in synthetic biology and cell engineering have paved the path for a new class of immunotherapies that employ chimeric antigen receptor (CAR)-engineered NK cells. These CAR-NK cells combine the intrinsic cytotoxicity of NK cells with the antigen-specific targeting capacity of CAR constructs, yielding precise and strong anti-tumor action. In contrast to CAR-T cells, CAR-NK therapies do not require strict HLA matching and have a lower risk of GVHD and cytokine release syndrome. The latest developments have included KIR engineering into the creation of CAR-NK cells as described in Table 7. Silencing or altering inhibitory KIRs can increase NK cell cytotoxicity, particularly in transplant circumstances involving KIR-HLA mismatches. Alternatively, adding synthetic activating receptors or increasing natural KIR-HLA connections might increase CAR-NK cell persistence and tumour selectivity as shown in Figure 5 [62]. CRISPR-Cas9 genome editing has been used to remove inhibitory KIR genes or introduce CAR constructs at specified genomic loci, allowing for the creation of uniform, highly powerful, and long-lasting CAR-NK cell populations. The conceptual workflow of CAR-NK cell development, including KIR editing and CAR insertion, is illustrated in Figure 6. These modified cells can be grown ex vivo and frozen as cryopreserved "off-the-shelf" allogeneic therapy. Early-phase clinical studies utilizing CAR-NK treatments have yielded encouraging results in the treatment of hematologic cancers, including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma. Importantly, CAR-NK infusions have shown significant anti-tumor activity with little toxicity. Synthetic biology has aided the production of NK cell lines, such as NK-92, that have been created with customized KIR profiles to imitate donor-specific alloreactivity. These modified cell lines can be tested systematically to increase GVL activity while lowering the danger of GVHD [63].

Table 7. Emerging KIR-based innovations in synthetic NK cell therapy.

Strategy	Description	Clinical Application	Status	Reference
CAR-NK Cells	NK cells engineered with tumor-specific CARs	Targeted immunotherapy in HSCT recipients	Phase I/II trials	[62]
CRISPR KIR Editing	Silencing of inhibitory KIRs	Enhanced NK cytotoxicity	Preclinical	[63]
Synthetic KIR Agonists/Antagonists	Small molecules to modulate KIR signaling	GVHD mitigation, GVL enhancement	Experimental	[64]
NK-92 Cell Line Engineering	Stable NK line modified with KIR repertoire	Universal donor model	Under development	[65]

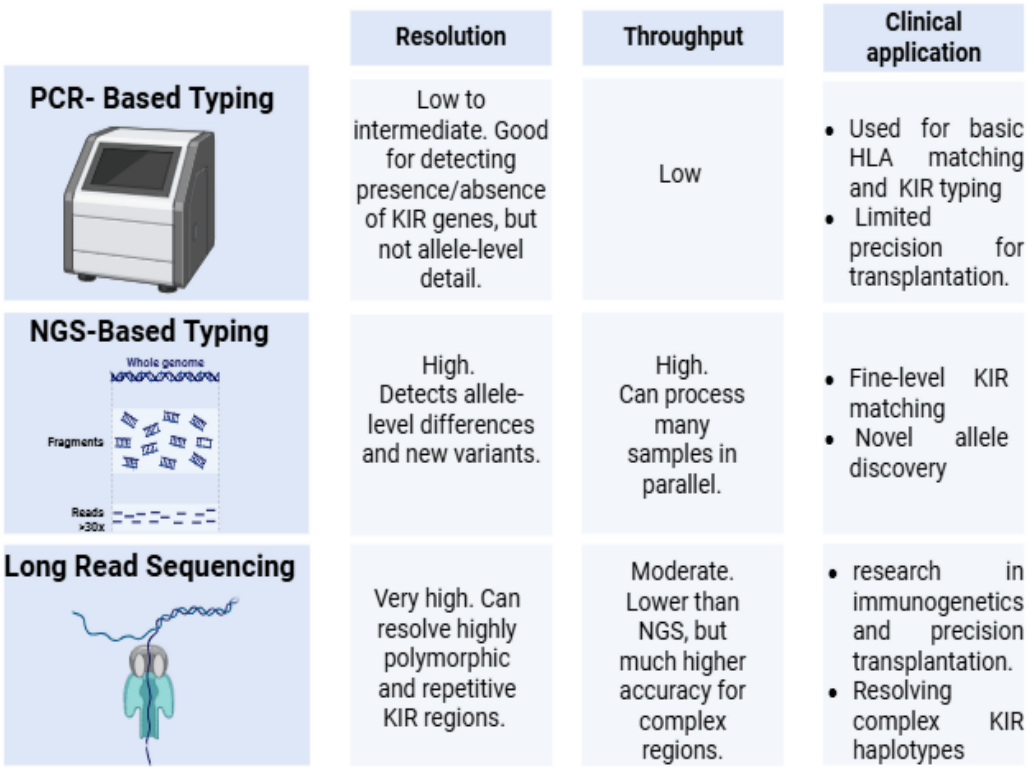

Figure 5. Overview of KIR typing methodologies. The figure compares PCR-based, NGS-based, and long-read sequencing platforms in terms of resolution, throughput, and clinical application.

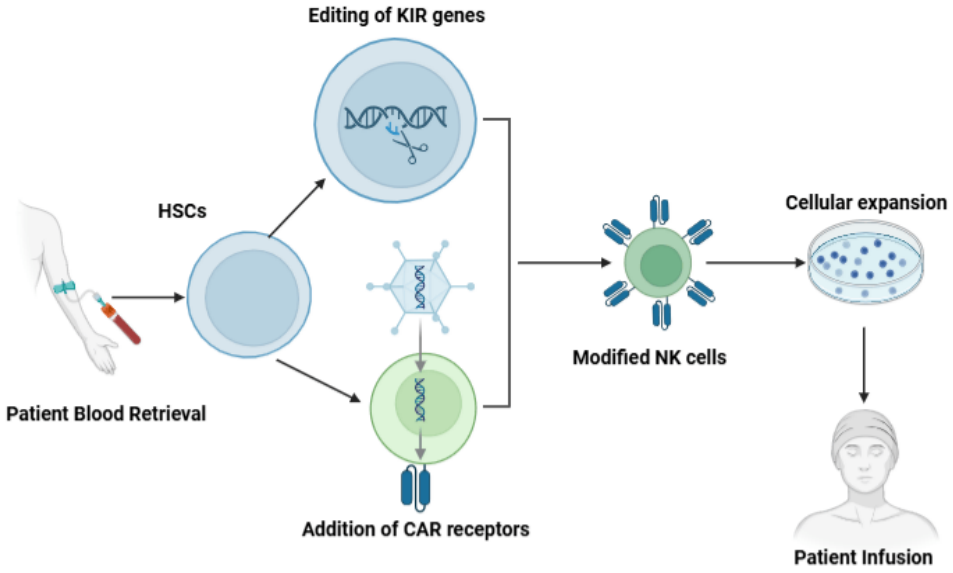

Figure 6. Conceptual illustration of CAR-NK cell development. The schematic depicts KIR gene editing, CAR insertion, and NK cell expansion for clinical use.

The following section discusses existing clinical gaps and the difficulty of incorporating KIR data into conventional HSCT regimens.

11. Clinical Guidelines and Translational Gaps

Synthetic biology has also assisted in the making of NK cell lines, such as NK-92, that have been created with customized KIR profiles to imitate donor-specific alloreactivity. These modified cell lines can be tested systematically to increase GVL activity while lowering the danger of GVHD. Variation in genotyping technologies and reference databases is a substantial challenge, resulting in inconsistent KIR data presentation and categorization. Furthermore, many transplant centres lack the equipment and specialized skills required for high-resolution KIR typing and reliable findings interpretation. The paucity of large-scale, prospective, randomized clinical trials comparing KIR-guided donor selection to traditional HLA-based matching impedes wider clinical implementation [66]. Consensus-building activities are being implemented to close the gap. Organizations like the European Society for Blood and Marrow Transplantation (EBMT), the National Marrow Donor Program (NMDP), and the World Marrow Donor Association (WMDA) are

working to provide standardized protocols for KIR data reporting and clinical applications. Emerging translational approaches, such as inhibitory-KIR/NKG2A blockade, KIR-informed donor selection, adoptive CAR-NK therapies, NK-cell engagers, cytokine-based expansion, and KIR gene editing, show promise for increasing GVL while reducing GVHD. Still, each requires careful timing, combination strategy, and prospective validation in HSCT settings. In addition, transplant outcomes are being evaluated across varied populations using multi-institutional registries and meta-analyses to verify genotype-based classification models. Another translational problem is integrating KIR data into digital systems to enable real-time donor matching. Although HLA registries have developed search algorithms, few systems presently support KIR loci. Advances in computational modelling and artificial intelligence may someday allow for the seamless inclusion of KIR parameters with established immunogenetic markers. Finally, the implementation of KIR-guided methods will be determined by evidence of improved patient outcomes, cost-effectiveness evaluations, and the availability of genotyping technology in a variety of resource contexts, as described in Table 8 [67].

Table 8. Barriers and solutions for KIR-based clinical integration in HSCT.

Barrier	Description	Proposed Solution	Implementation Stage	Reference
Lack of Standardized Guidelines	Absence of universal KIR inclusion criteria	International consensus via registries	Ongoing	[68]
Genotyping Platform Variability	Diverse methods and resolutions	Harmonized protocols, inter-lab QA	In progress	[69]
Limited Clinical Trials	Insufficient prospective comparative data	Multi-center RCTs and observational studies	Proposed	[70]
Incomplete Registry Integration	KIR data is often not searchable in registries	AI-enhanced matching systems	Under development	[71]

12. Conclusion

KIR-HLA interactions influence NK cell education and function following HSCT. Current evidence indicates that donor KIR genotype, KIR-ligand compatibility, and NK receptor reconstitution have a significant impact on GVL activity, GVHD risk, and immunological recovery. CMV-driven NK remodelling and epigenetic regulation contribute to the diversity and longevity of NK responses after transplantation. Emerging techniques, such as KIR-guided donor selection, NK checkpoint blockage, CAR-NK treatments, and NK-cell engagers, show promise for improving GVL while reducing GVHD. However, standardized methods, prospective clinical studies, and integrated multi-omics approaches are still necessary to put these discoveries into practice. Overall, KIR-based immunogenetics has considerable promise to improve HSCT outcomes and guide future personalized transplant methods.

Conflict of Interest

The authors confirm that the work presented in this paper was not impacted by any known conflicting financial or personal interests.

Generative AI Statement

The authors declare that no AI tools were used in the creation of this manuscript.

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