Influence of KIR and NK Cell Reconstitution in the Outcomes of Hematopoietic Stem Cell Transplantation

Fei Gao1,2,3, Yishan Ye1,2,3, Yang Gao1,2,3, He Huang1,2,3* and Yanmin Zhao1,2,3*

1 Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, 2 Institute of Hematology, Zhejiang University, Hangzhou, China, 3 Zhejiang Engineering Laboratory for Stem Cell and Immunotherapy, Hangzhou, China

Natural killer (NK) cells play a significant role in immune tolerance and immune surveillance. Killer immunoglobin-like receptors (KIRs), which recognize human leukocyte antigen (HLA) class I molecules, are particularly important for NK cell functions. Previous studies have suggested that, in the setting of hematopoietic stem cell transplantation (HSCT), alloreactive NK cells from the donor could efficiently eliminate recipient tumor cells and the residual immune cells. Subsequently, several clinical models were established to determine the optimal donors who would exhibit a graft-vs.-leukemia (GVL) effect without developing graft-vs.-host disease (GVHD). In addition, hypotheses about specific beneficial receptor-ligand pairs and KIR genes have been raised and the favorable effects of alloreactive NK cells are being investigated. Moreover, with a deeper understanding of the process of NK cell reconstitution post-HSCT, new factors involved in this process and the defects of previous models have been observed. In this review, we summarize the most relevant literatures about the impact of NK cell alloreactivity on transplant outcomes and the factors affecting NK cell reconstitution.

Keywords: KIR, NK cell reconstitution, hematopoietic stem cell transplantation, GVHD, infection, relapse

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective therapy for patients with hematological malignancies. However, relapse, graft-vs.-host disease (GVHD), and infections remain the main causes of treatment failure (1–4). Potential strategies to prevent GVHD and even infections while sparing the graft-vs.-leukemia (GVL) effect have attracted extensive attention. Natural killer (NK) cells, which are a major type of innate lymphocytes, are being researched in this context.

NK cells constitute 5–15% of human peripheral blood lymphocytes (5, 6) and possess the abilities of cytotoxic lysis and rapid cytokine secretion without prior antigen presentation (7, 8). These functions are regulated by various types of receptors expressed on NK cells manifesting multiple functions either activating or inhibitory (9–11) (Table 1). Among the NK cell receptors, the killer immunoglobin-like receptor (KIR) is one of the major factors that mediate self-tolerance and anti-tumor/infection responses.
It is well established that KIR genes are located on chromosome 19q13.4 (12). Based on their various structures (the number of extracellular immunoglobulin domains (D) and the long (L) or short (S) tails), 16 KIR genes (including two pseudogenes (P), KIR2DP1 and KIR3DP1) have been classified into four groups (KIR2DL1-5, KIR3DL1-3, KIR2DS1-5, and KIR3DS1). Six genes with short tails are activating KIR genes that encode activating receptors, while the eight genes with long tails are inhibitory KIR genes encoding inhibitory receptors. KIRs could be divided into haplotype A and B according to the activating genes on them. Haplotype A has only one activating gene, KIR2DS4, whereas haplotype B possesses up to five activating KIR genes, including KIR2DS1, 2, 3, 5, and 3DS1 (Figure 1). Thus, the A/A genotype is defined as homozygous for A haplotypes, and the B/x genotype consists of at least one B haplotype. Finally, according to the specific KIR gene locus on the chromosome, a centromeric (Cen) and telomeric (Tel) KIR haplotype and genotype are further determined (13–15). Five inhibitory and three activating KIRs recognize specific class I HLA (A, B, or C) ligands, with the inhibitory KIR2DL1 recognizes group 2 HLA-C alleles, KIR2DL2 and KIR2DL3 recognize group 1 HLA-C alleles, KIR3DL1 recognizes group 2 HLA-C alleles, and KIR3DL2 recognizes HLA-A3/-A11 alleles. Moreover, activating KIR2DS1, KIR2DS2, and KIR2DS4 recognize HLA-C2, C1, A11, respectively (15). The ligands of the remaining KIRs remain unknown.

As KIR genes and human leukocyte antigen (HLA) genes are located on different chromosomes, autologous KIR receptor-ligand mismatch may exist (16). Normally, NK cells acquire self-tolerance and functional competence through the education process, in which inhibitory KIRs could be inhibited by self-HLA ligands and activated in a non-self HLA environment. Besides, the decreased responsiveness of activating KIRs in the presence of their cognate ligands also prevents autoimmunity (17–23) (Figure 2A). Importantly, infected and/or tumor cells may express inhibitory KIR ligands insufficiently or express activating ligands that may activate NK cells (24–31).

As the first reconstituted lymphocyte subset after transplantation (32, 33), NK cells play a critical role in controlling early relapse and infections. They also possess the ability to eliminate recipient T cells and antigen-presenting cells (APCs), to prevent graft failure and GVHD (34–38) (Figure 2B). Three models were established historically in an attempt to optimize donor selection for HSCT based on KIR (Figure 2A). The Perugia group in Italy firstly proposed the donor-recipient KIR ligand-ligand model (also known as KIR ligand model) solely based on the HLA phenotype of the donor and recipient. The KIR ligand incompatibility in the GVH direction was defined as the absence in recipients of donor class I allele group(s) recognized by KIRs. Those authors observed that the HLA haplotype-mismatched transplants reduced the rejection and relapse rate and prevented GVHD in patients with acute myeloid leukemia (AML) (36). Subsequently, the second model (named receptor-ligand model or missing ligand model) was raised by Leung et al. based on the compatibilities between the recipient HLA and donor inhibitory KIR. This model focused on donor KIR instead of donor HLA and could, therefore, be used in both HLA-matched and HLA-mismatched transplants. The results of that study suggested that the receptor-ligand model better predicted the risk of primary disease relapse, especially for lymphoid malignancies, compared with the ligand-ligand model (39). Subsequently, with a deeper understanding of KIR haplotypes, the third model analyzed and compared the KIR genotypes of different donors. Cooley et al. showed that unrelated donors with KIR-B haplotypes conferred a significant relapse-free survival (RFS) benefit to patients with AML undergoing T cell-replete HSCT (40). Based on the three models described above, numerous studies have been carried out to explore the impact of NK cell alloreactivity. Clinical results obtained from KIR ligand model, receptor ligand model and KIR haploype and gene model were summarized in Tables 2–4, respectively. Nevertheless, the results were controversial, and several key questions remained regarding NK cell biology post-HSCT. What are the exact effects of NK cell alloreactivity on patients after HSCT? How do NK cells reconstitute post-HSCT and which factors may interfere with the reconstitution process? This review summarizes the latest literature on this important topic and offer some instructive hypothesis.

KIR AND TRANSPLANT OUTCOMES

NK Cell Alloreactivity and GVHD

GVHD is an important complication of HSCT with high morbidity and mortality in which allogeneic donor immune cells are activated by APCs and then recognize and attack the host tissue (105). Removing donor T cells from grafts reduces the occurrence of GVHD, while it also elevates the risk of graft failure and disease relapse (106–108).

As another component of immune cells, previous murine studies suggested that adoptive transfer of interleukin-2 (IL-2)-activated SCID NK cells with donor bone marrow cells
promoted engraftment in allogenic hosts with no signs of GVHD (109). Later, Asai et al. reported that hosts receiving MHC-incompatible bone marrow and spleen cells (as a source of T cells) rapidly succumbed to acute GVHD, while hosts who additionally received IL-2-activated donor NK cells on day 0 experienced a significant improvement in survival because of the lower incidence of severe GVHD. They further demonstrated that that the protective effect on GVHD was dependent on the transforming growth factor-beta (TGF-β) and could be abrogated by an anti-TGF-β antibody (35). Moreover, Ruggeri et al. showed that pre-transplant alloreactive Ly49 (Ly49 receptors recognize major histocompatibility complex (MHC) class I molecules in mice, which is analogous to KIR in humans) ligand-mismatched donor NK cell transfusion successfully eliminated host tumor cells and protected against GVHD by depleting host APCs. In contrast, hosts receiving bone marrow grafts without NK cell infusion died of GVHD, and non-alloreactive Ly49 ligand matched NK cell infusion did not provide protection against GVHD (36). Consistently, subsequent studies also found that donor alloreactive NK cells suppressed GVHD by inhibiting T cell proliferation and activation (37, 110). However, the protective role of NK cells in GVHD pathogenesis has also been challenged. Pre-clinical evidence from a xenogeneic model showed that an in vitro IL-2-activated human NK cell infusion promoted GVHD in SCID mice via the production of cytokines such as IFN-γ and tumor necrosis factor-α (TNF-α) (111, 112). Accordingly, GVHD was inhibited after the administration of anti-IFN-γ and depletion of Poly I:C-activated NK cells in murine studies (113, 114).

In patients with hematological malignancies, a purified (115, 116) or cytokine-induced (117–121) donor NK cell transfusion was also well tolerated and seldom induced severe GVHD (grade III-IV acute GVHD or moderate-to-severe chronic GVHD). More recently, a pilot study suggested that, after haplo-HSCT, patients with refractory AML who received a donor NK cell infusion experienced a significantly lower grade II-IV GVHD than did those without NK cell infusion (122). In contrast, Shah et al. observed that patients who received a donor...
IL-15/4-1BBL-activated NK cell infusion after T cell-depleted (TCD) stem cell transplantation experienced a high risk of GVHD (123).

In addition to the technique of adoptive transfer, many studies have analyzed the effects of innate donor-recipient NK cell alloreactivity on GVHD in a clinical setting. The majority of studies did not report a significant association between these parameters (41–44, 46, 47, 50, 51, 54–56, 59, 65, 66, 79, 81, 83, 87–89, 91–93, 97, 98, 102, 104), while some reported a protective effect (70, 74, 76). Moreover, several studies found that KIR ligand mismatch or receptor-ligand mismatch increased the risk of GVHD (45, 57, 60, 64, 68, 80). Accordingly, two studies performed in China that applied the ‘Peking protocol’ for HSCT using the granulocyte-colony stimulating factor (G-CSF)-mobilized graft containing a high dose of T cells observed promotive effects of NK cell alloreactivity on GVHD (48, 49).

It is not entirely clear why the reconstituted alloreactive NK cells were unable to prevent GVHD as the adoptively transferred NK cells. Studies have indicated that this discrepancy was probably attributable to the impaired function of early reconstituted NK cells. Shilling et al. first observed that a period of several months or even years was required for the recipient to reconstitute an NK cell repertoire resembling that of the donor (124). Vago et al. also suggested that the NK cells that were reconstituted early after transplantation were immature and exhibited compromised cytotoxicity (125). In addition, NK cell reconstitution is affected by graft composition. Patients receiving more T cells in grafts experience a faster T cell reconstitution (126, 127), while the absolute number of reconstituted NK cells and KIR expression are impaired by the co-grafted T cells (127–130). Other than NK cells, nearly 5% of CD8+ T cells, 0.2% of CD4+ T cells, and 10% of γδ T cells in the peripheral blood also express KIRs (131–133). Therefore, it is possible that the potential beneficial effects of alloreactive NK cells are overwhelmed by the strong alloreactive T cell response. In addition, it was observed that NK cells generated more IFN-γ in the presence of T cells in grafts, leading to a higher occurrence of acute GVHD (aGVHD) (130). Moreover, post-transplant immune suppression also exerted negative effects on NK cell reconstitution (134, 135).

Regarding specific genotypes, some studies have reported that KIR haplotype B donors afforded a significantly reduced risk of GVHD (60, 63, 86, 96). Consistent with these findings,
were efficient in killing allogenic dendric cells in the setting
Sivori et al. suggested that donor NK cells expressing KIR2DS1
TCD*: in-vivo TCD.

Davies et al. (41) 175 Mixed URD TCD*, TCR
Giebel et al. (42) 130 Mixed URD TCD# KIR ligand mismatch: higher OS and DFS, lower TRM
Schaffer et al. (43) 190 Mixed URD TCD*, TCD# KIR ligand mismatch: higher IRM and TRM, and lower OS
Elmaagacli et al. (44) 236 CML MSO, URD TCR
Yabe et al. (45) 1489 Mixed URD TCD#, TCR
Verneris et al. (46) 716 Pediatric AL TCD#, TCR
Ruggeri et al. (47) 112 AML HRD TCD*
Huang et al. (48) 116 Mixed HRD TCD# KIR ligand mismatch: higher aGVHD and lower relapse and CMV reactivation,
Zhao et al. (49) 64 Mixed HRD TCD# KIR ligand mismatch: higher aGVHD;
Michaelis et al. (50) 57 Mixed HRD TCD* KIR ligand mismatch: lower DFS
Mancusi et al. (51) 161 AML, ALL HRD TCD* TCD*+/Treg/Tcon
Yahng et al. (52) 100 AML HRD TCD# KIR ligand mismatch (HVG); higher relapse and CMV reactivation, lower DFS
Zhao et al. (53) 180 Mixed HRD TCD# KIR ligand match: lower CMV reactivation rate and higher IFN-γ expression
Wanquet et al. (54) 144 Mixed HRD TCD# KIR ligand mismatch: lower relapse and higher PFS (no CR group)
Shimoni et al. (55) 444 AML, ALL HRD TCD# KIR ligand mismatch: a trend of higher relapse (AML), lower OS

MSD, matched sibling donor; URD, unrelated donor; HRD, haploidentical related donor; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; TCD, T cell depleted; TCR: T cell replete; Treg, regulatory T cells; Tcon, conventional T cells; aGVHD: acute graft vs. host disease; cGVHD: chronic graft vs. host disease; OS, overall survival; DFS, disease-free survival; EFS, event-free survival; IRM: infection-related mortality; TRM: transplant-related mortality; CMV: cytomegalovirus.

TABLE 2 | Impact of KIR on clinical outcomes in KIR ligand model.

References N Disease Donor Graft manipulation Clinical outcomes
Ruggeri et al. (36) 92 AML, ALL HRD TCD* KIR ligand mismatch; higher EFS and OS, lower relapse (AML)
Davies et al. (41) 175 Mixed URD TCD*, TCR KIR ligand mismatch; lower aGVHD
Giebel et al. (42) 130 Mixed URD TCD# KIR ligand mismatch; higher OS and DFS, lower TRM
Schaffer et al. (43) 190 Mixed URD TCD*, TCD# KIR ligand mismatch; higher IRM and TRM, and lower OS
Elmaagacli et al. (44) 236 CML MSO, URD TCR KIR ligand mismatch; lower molecular relapse
Yabe et al. (45) 1489 Mixed URD TCD#, TCR KIR ligand mismatch: higher aGVHD and lower OS (HLA-C mismatched transplants)
Verneris et al. (46) 716 Pediatric AL TCD#, TCR KIR ligand mismatch: no significant impact on OS, DFS, relapse, TRM, or aGVHD.
Ruggeri et al. (47) 112 AML HRD TCD* KIR ligand mismatch; lower relapse (CR group), higher EFS, and lower risk of relapse or death
Huang et al. (48) 116 Mixed HRD TCD# KIR ligand mismatch: higher aGVHD and relapse, lower OS
Zhao et al. (49) 64 Mixed HRC TCD# KIR ligand mismatch: higher aGVHD;
Michaelis et al. (50) 57 Mixed HRD TCD* KIR ligand mismatch: lower EFS (AML)
Mancusi et al. (51) 161 AML, ALL HRD TCD* TCD*+/Treg/Tcon NK-alloreactive donors: lower relapse and higher EFS (AML)
Yahng et al. (52) 100 AML HRD TCD# KIR ligand mismatch (HVG); higher relapse and CMV reactivation, lower DFS
Zhao et al. (53) 180 Mixed HRD TCD# KIR ligand match: lower CMV reactivation rate and higher IFN-γ expression
Wanquet et al. (54) 144 Mixed HRD TCD# KIR ligand mismatch: lower relapse and higher PFS (no CR group)
Shimoni et al. (55) 444 AML, ALL HRD TCD# KIR ligand mismatch: a trend of higher relapse (AML), lower OS

NK Cell Alloreactivity and Infection

Infections are especially challenging for patients after HSCT because of the immunological derangement caused by multiple factors, including an intensive conditioning regimen, immunosuppressive agents, and other complications, such as GVHD (137, 138).

Several studies have reported that patients receiving KIR ligand-mismatched transplants are more vulnerable to infections. Schaffer et al. first reported that KIR ligand mismatch was associated with an increased infection-related mortality (43). Similarly, results from Zhao et al. showed that recipients from the KIR ligand-mismatched group experienced a significantly higher cytomegalovirus (CMV) reactivation rate. Moreover, the percentage of interferon-gamma (IFN-γ)-expressing NK cells in the peripheral blood was significantly higher in the KIR ligand matched group 30 and 100 days post-HSCT compared with the KIR ligand-mismatched group (53). The higher level of IFN-γ secretion from the NK cells might trigger Th1 immune responses, antigen presentation cell activation, and macrophage killing (7, 8), leading to lower infection rate. While, KIR ligand mismatch may increase the risk of infection by eliminating recipient APCs by donor alloreactive NK cells (36).

Many studies have found that KIR-B genes protect patients with HSCT against infections and most of them were predominantly T cell replete (TCR) transplants (81, 84, 87, 96, 139, 140). Cook et al. first observed that KIR haplotype B donors exhibited a significant reduction in the rate of CMV reactivation in sibling allo-HSCT (139). Wu et al. and Zaia et al. reported that donors expressing higher numbers of activating KIRs were associated with a lower CMV reactivation rate (62, 84). Specifically, activating KIR2DS2 and KIR2DS4 may play a major protective role (84, 140). Importantly, transplantations from donors with KIR2DS1 correlated with better infectious control (51, 96). Mancusi et al. further demonstrated that the binding
of KIR2DS1 to HLA-C2 triggered pro-inflammatory cytokine production by alloreactive NK cells (51). Moreover, without a cognate ligand (HLA-C1) in recipients, donor KIR2DS2 was associated with a higher CMV reactivation rate after HLA-identical sibling HSCTs (81). Apart from CMV reactivation, the incidence of bacterial infections was also reduced when patients had KIR-B/x donors (87). In contrast with previous results, KIR2DS2 gene and Cen-B/x donors related to a higher incidence of CMV reactivation and infection-related mortality in TCD transplants (53, 106). The reasons for these differing results may be due to the different graft composition. As previously described, NK cells generate more IFN-γ in TCR transplants, which may benefit the infection control (130). Of notice, the activating KIR targets outside of HLA are largely unknown, and these clinical observations still need to be confirmed by definitive functional analysis in the future.

**NK Cell Alloreactivity and Relapse/Survival**

Primary disease relapse remains the main obstacle that hampers the long-term survival of patients with hematological malignancies. Previous experience showed that adoptive transfer of autologous NK cell for patients with tumors was safe but inefficient (141–145), probably because autologous NK cells could not overcome the inhibition mediated by
### TABLE 4 | Impact of KIR on clinical outcomes in KIR haplotype and gene model.

| References            | N  | Disease | Donor  | Graft manipulation | Clinical outcomes                                                                 |
|-----------------------|----|---------|--------|-------------------|-----------------------------------------------------------------------------------|
| Cooley et al. (40)    | 448| AML     | URD    | TCR               | KIR B/x donor: higher RFS and cGVHD                                                |
| Cook et al. (56)      | 220| Mixed   | MSD    | /                 | KIR2DS2: lower OS (HLA-C2C2 patients with myeloid diseases)                          |
| Verheyden et al. (57) | 65 | Mixed   | MSD    | TCD*, TCR         | Donor co-presenting KIR2DS1 and 2DS2: lower relapse                                 |
| Chen et al. (81)      | 131| Mixed   | MSD    | TCR               | KIR2DS2: higher CMV reactivation (HLA-C2C2 patients); Additional activating KIR genes in donor: higher OS and lower CMV reactivation |
| Yabe et al. (45)      | 1489| Mixed   | URD    | TCD#, TCR         | KIR2DS2: higher aGVHD<sup>3−4</sup> (HLA-C mismatched transplants)                 |
| Schellekens et al. (62)| 83 | Mixed   | MSD    | TCR               | Donor co-presenting KIR 2DS2 and 2DS4: lower CMV reactivation; Donor aKIR gene content ≥5: lower CMV reactivation |
| van der Meer et al. (83)| 70 | Mixed   | MSD    | TCD*              | KIR2DS2: higher LFS and lower relapse (HLA-C1C1 or HLA-C2C2 patients); KIR2DS5: lower LFS and higher relapse (HLA-C1C2 patients) |
| Ludajic et al. (60)   | 124| Mixed   | URD    | TCD#, TCR         | KIR2DS2: lower aGVHD<sup>2−3</sup> (HLA-C1C2 patients)                             |
| Zaia et al. (84)      | 211| Mixed   | MSD, URD| TCR               | Donor co-presenting KIR 2DS2 and 2DS4: lower CMV reactivation; Donor aKIR gene content ≥5: lower CMV reactivation |
| Wu et al. (62)        | 48 | Mixed   | URD    | TCD#              | High aKIRs group; lower CMV reactivation rate                                        |
| Gagné et al. (86)     | 264| Mixed   | URD    | TCR               | KIR B/x donor: lower aGVHD<sup>3−4</sup> (HLA identical pairs with myeloid disease) |
| Bao et al. (85)       | 75 | Mixed   | URD    | TCD#              | KIR B/x donor: higher OS                                                             |
| Venstrom et al. (88)  | 1087| Mixed | URD    | TCD*, TCR         | KIR3DS1: lower aGVHD<sup>2−4</sup>; KIR3DS1: lower aGVHD<sup>2−4</sup>, TRM and mortality (AML, CML and ALL) |
| Wu et al. (66)        | 116| Mixed   | URD    | TCD#, TCR         | KIR2DS2: higher relapse, lower OS and DFS (myeloid cohort); More numbers of activating KIR genes in donor: higher relapse |
| Tomblyn et al. (67)   | 116| Mixed   | URD    | TCD*, TCR         | KIR B/x donor: lower bacterial infections by day 180                                |
| Cooley et al. (88)    | 1409| AML, ALL| URD    | TCR               | KIR B/x donor: lower relapse and higher DFS (AML); Cen-B/B vs. Cen-BA or AA: lower relapse and higher DFS (AML); Tel-B/x vs. Tel-AA: lower relapse (AML); B content ≥ 2: lower relapse (AML) |
| Venstrom et al. (89)  | 1277| AML    | URD    | TCD*, TCR         | Donor KIR2DS1 with HLA-C1/x patients vs. with HLA-C2C2 patients; lower relapse; KIR3DS1: higher OS |
| Zhou et al. (67)      | 219| Mixed   | MSD    | /                 | Cen-B/x donor: higher OS, RFS and lower relapse                                      |
| Impola et al. (90)    | 134| Mixed   | MSD    | /                 | KIR 2DL2 or KIR 2DS2: better RFS (AML)                                              |
| Bao et al. (91)       | 210| Mixed   | URD    | TCD#              | KIR B/x donor: higher OS, RFS and lower NRM (AML and MDS); Cen-B/x donor: higher OS, RFS (AML and MDS at standard risk) |
| Cardozo et al. (70)   | 50 | Mixed   | MSD    | TCR               | KIR2DS2: lower OS and EFS                                                           |
| Bachanova et al. (92) | 614| NHL     | URD    | TCD#, TCR         | KIR B/x donor: lower relapse and better PFS (HLA matched transplants)               |
| Kamenaric et al. (93) | 111| Mixed   | MSD, URD| TCD#              | KIR2DS4 (neg vs. pos): no impact on GVHD (MDS)                                      |
| Hosokai et al. (94)   | 106| Mixed   | MSD, URD| TCR               | KIR B/x donor: higher aGVHD<sup>3−4</sup> (more evident in HLA mismatched transplants) |
| Neuchel et al. (72)   | 1446| Mixed  | URD    | TCR               | KIR2DS2: higher OS and DFS (HLA-C2C2 patients); KIR2DS1: lower relapse but higher TRM (HLA-C2C2 patients), KIR2DS3: lower relapse (HLA-C2C2 patients) |
| Gaafar et al. (74)    | 87 | Mixed   | MSD    | TCR               | KIR2DS2: higher OS and DFS (HLA-C2C2 patients); KIR2DS1: lower relapse but higher TRM (HLA-C2C2 patients), KIR2DS3: lower relapse (HLA-C2C2 patients) |
| Sahin et al. (95)     | 96 | AML, CML| MSD    | TCR               | KIR B/x donor: higher cGVHD                                                          |
| Heatley et al. (96)   | 152| Mixed   | MSD    | TCR               | KIR2DS2: higher OS (AML); Cen-B/x donor: higher OS (AML) and lower aGVHD<sup>2−4</sup> (AML); Tel B/x donor: lower CMV reactivation |
| Babor et al. (97)     | 317| Pediatric ALL | URD    | TCD#, TCR         | Higher ct-KIR score: lower relapse                                                  |
| Tordai et al. (98)    | 314| Mixed   | MSD, URD| TCR               | The combination of KIR2DS1 donor with HLA-C2 pos patients: higher OS                |

(Continued)
TABLE 4 | Continued

| References | N  | Disease | Donor | Graft manipulation | Clinical outcomes |
|------------|----|---------|-------|--------------------|-------------------|
| Nakamura et al. (69) | 288 | AML | MSD, URD | TCD⁺, TCD# | CMV reactivation: lower relapse and higher NRM (more evident in KIR B/x donor or when donor presenting KIR2DS1) |
| Bultitude et al. (100) | 119 | AML | URD | TCD, TCR | Cen-B/x donor: lower OS and NRM, higher IRM |
| Weisdorf et al. (101) | 2662 | AML | URD | TCD⁺, TCR | KIR B/x donor: lower relapse and higher LFS (RIC) |
| Vennieris et al. (46) | 716 | Pediatric AL | URD | TCD⁺, TCR | KIR gene content: no significant impact on OS, DFS, relapse, TRM, or aGVHD |
| Zhao et al. (49) | 64 | Mixed | HRD | TCD⁺ | KIR2DS3: higher aGVHD and cGVHD; KIR2DS5: higher aGVHD |
| Symons et al. (102) | 86 | Mixed | HRD | TCD⁺ | KIR B/x donor: lower NRM and higher OS, EFS (KIR AA patients) |
| Chen et al. (76) | 84 | Mixed | HRD | TCD⁺ | KIR2DS2: higher OS (lymphoid cohort); KIR2DS1: higher GVHD (lymphoid cohort) |
| Michaelis et al. (50) | 57 | Mixed | HRD | TCD⁺ | KIR B/x donor: lower relapse |
| Zhao et al. (77) | 97 | CML | HRD | TCD⁺ | KIR2DS3: lower EFS and OS, higher TRM; KIR2DS5: higher EFS and OS, lower TRM; KIR B/x donor: higher aGVHD³⁻⁴ |
| Oevermann et al. (103) | 85 | Pediatric ALL | HRD | TCD⁺ | KIR B/x donor: lower relapse and better EFS; High donor KIR-B content: lower relapse and better EFS |
| Mancusi et al. (51) | 161 | AML, ALL | HRD | TCD⁺ | Tel B/x vs. Tel AA: lower NRM and higher EFS (NK-alloreactive donors) KIR2DS1/3DS1: lower NRM and higher EFS (NK-alloreactive donors) KIR 2DS1 binding to HLA C2: increased inflammatory cytokine |
| Zhao et al. (53) | 180 | Mixed | HRD | TCD⁺ | KIR2DS2: higher CMV reactivation |
| Solomon et al. (79) | 208 | Mixed | HRD | TCD⁺ | KIR B/x donor with 2DS2 vs. KIR B/x donor without 2DS2: higher OS and DFS, lower relapse and NRM; KIR B/x donor with 2DS2 vs. KIR A/A donor: higher OS and DFS, lower NRM |
| Perez-Martinez et al. (104) | 192 | Pediatric mixed | HRD | TCD⁺, TCD# | KIR AA donor: higher relapse and lower DFS |

pos: positive; neg: negative; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; NRM: non-relapse mortality. TCD⁺: ex-vivo TCD; TCD⁺: in-vivo TCD.

tumor cells expressing self-HLA. In contrast, allogenic (117), especially haploidentical, donor NK cell infusion demonstrated wide prospects in the salvage treatment (115, 120, 121) and prophylactic treatment (118, 119) of patients with hematological malignancies. In allo-HSCT, whether the reconstituted alloreactive NK cells prevent the disease relapse remains controversial.

In HLA-mismatched transplants, the Perugia group first observed that, in the context of T cell depletion, high stem cell dose, and absence of post-transplant immune suppression, KIR ligand mismatch reduced the risk of relapse and markedly improved survival in patients with AML, but not in those with acute lymphoblast leukemia (ALL) (36). This protective effect on relapse or survival was supported by many clinical studies (42, 44, 47, 51, 54), especially in myeloid disease (44, 47, 51) and transplants with TCD grafts (42, 47, 51, 54). However, conflicting results stemmed from many studies that failed to replicate these results (39, 46, 58, 102), and some even reached the opposite conclusions (41, 43, 45, 48, 50, 55).

Studies using the receptor-ligand model including HLA-matched donor-recipient pairs also reported conflicting results. Leung et al. first reported that the receptor-ligand model was more accurate than the KIR ligand model when predicting the risk of relapse, especially for lymphoid malignancies. Moreover, the potency of the relapse protection positively correlated with the number of receptor-ligand mismatch pairs (39). Subsequently, the protective effect of receptor-ligand mismatch has been confirmed by many investigations (58, 59, 66, 69, 71, 73, 76, 79, 80). Moreover, a survival advantage was also observed in patients with receptor-ligand mismatch compared with receptor-ligand matched pairs (59, 66, 69–71, 73, 76, 79). However, several other studies described opposite results (63, 64, 75, 77, 78). Of notice, two studies from Japan observed that the lack of the HLA-C2 ligand for donor inhibitory KIR afforded relapse protection in patients with AML and chronic myeloid leukemia, but increased the relapse rate in patients with ALL (73, 75). To date, no plausible explanation has been put forward for this disparity in relapse.

In contrast to the controversial results described above, transplantations from KIR haplotype B donors achieved greater agreement. Cooley et al. observed that patients with AML with KIR-B/x donors experienced a 30% improvement in RFS compared with those with A/A donors (40). Subsequently, many further investigations confirmed this beneficial effect of the KIR-B haplotype on relapse and survival in patients with hematological malignancies (50, 51, 57, 67, 72, 76, 79, 81, 85, 88–92, 96, 98, 101–104). Five of these studies reported that the protection effects mainly existed in the KIR Cen-B locus (67,
NK cells, and NK cells are barely detectable in the peripheral blood. Subsequently, the reconstituted NK cells gradually recover and express high levels of CD56 and NKG2A. Around 60 days after transplantation, the KIR expression returns to normal. The expression of CD56 and NKG2A gradually decreases and becomes stable at 9–12 months post-transplantation. Other receptors expressed on NK cells, such as DNAM-1 and 2B4, also require several months to return to normal (152). In summary, post-transplantation NK cell reconstitution is a long-term process (124, 125, 152).

**KIR Education: From Anergic to Responsive**

As described earlier, the random combination of KIR receptor and HLA ligand can exist in healthy individuals. However, the autoimmune attack is inhibited because each NK cell expresses at least one self-inhibitory receptor. To avoid autoactivity, NK cells must undergo an education process: NK cells expressing inhibitory KIR for self-HLA ligand (self-KIR) are educated, which means that these cells can be inhibited by self-inhibitory signals and become alloreactive against self-HLA-deficient targets. In contrast, NK cells expressing an inhibitory KIR that lacks a self-HLA ligand (non-self KIR) are uneducated, which means that they are tolerant to the self but also to infected or malignant cells (19, 21).

In the last decades, studies on KIR education have much extended our knowledge of NK cell function. After transplantation, most reconstituted NK cells express a donor-like KIR repertoire that is significantly different from that of recipient NK cells prior to transplantation (124, 151). Therefore, reconstituted NK cells expressing donor KIR may exert alloreactivity in recipients, or become anergic, as recipients may not present the cognate HLA (Figure 3). Foley et al. and Björklund et al. observed that reconstituted NK cells with non-self KIR remained tolerant, while those with self KIR acquired better functions after transplantation (65, 153). However, Yu et al. reached the opposite conclusion that alloreactive NK cells broke the self-tolerance and displayed functional capacities in the first 3 months, then gradually acquired self-tolerance by day 100 after transplantation (154). Rathmann et al. also suggested that alloreactive NK cells were increased in the peripheral blood and exhibited a GVH effect in the early period after transplantation (155). One possible explanation for this observation is that the infusion of a megadose of donor CD34+ cells may create a transient donor dominant HLA environment in recipient bone marrow, and the early reconstituted NK cells expressing non-self KIR for the recipient may become educated by donor HLA and acquire functions (156).

After migration to a recipient-dominant environment, reconstituted NK cells may gradually lose their responsiveness. In murine studies, it was observed that mature NK cells from major histocompatibility complex (MHC) class I-deficient mice become hyporesponsive after transfusion into MHC class I-deficient mice. Conversely, anergic NK cells from MHC class I-deficient mice acquired functions after exposure to the MHC class I-deficient environment (157, 158). Using a murine

**NK CELL RECONSTITUTION AFTER TRANSPLANTATION**

**Maturation and Differentiation of NK Cells**

NK cells are derived from the CD34+ hematopoietic stem and precursor cells in the bone marrow, which then migrate to the periphery (147). Recent evidence suggested that not only the bone marrow, but also secondary lymphoid tissues contribute to the development of NK cells (148). According to the surface expression of CD56, NK cells could be divided into two main subtypes: CD56bright and CD56dim NK cells. CD56bright NK cells exist mainly in lymph nodes and tonsils, while CD56dim NK cells, the more mature subset transformed from CD56bright NK cells, are dominant in the peripheral blood (7, 147, 149, 150). CD56bright and CD56dim NK cells are equipped with distinct functions. The former population responds rapidly to interleukin-mediated stimulation with proliferation and cytokine secretion, while the latter population displays higher cytolytic capacity and lower proliferation (7, 8, 149). During the process of maturation, CD94/NKG2A is the first receptor that is expressed on immature NK cells. Together with the downregulation of CD56 expression, NK cells upregulate CD16 expression, lose NKG2A, and acquire KIR receptors. Finally, a subset of CD56dim cells continue to differentiate and express CD57, together with an increased KIR expression and a completely abolished proliferative ability (150, 151).

In HSCTs with post-transplant cyclophosphamide (PT-Cy) as GVHD prophylaxis, NK cells experience two waves of expansion. After graft infusion, peripheral NK cells and T cells (mainly mature cells from the donor) were detectable at very low levels. PT-Cy administration results in a further decrease in T cells and NK cells, and NK cells are barely detectable in the peripheral blood.
transgenic model of HLA-B*27:05 exhibiting the Bw4 ligand for KIR3DL1. Boudreau et al. observed similar results in stem cell transplantation. CD34+ cells from KIR3DL1+ donors were transfused to B27 Tg+ and Tg− mice, respectively. A functional analysis suggested that the most cytotoxic responsive cells were KIR3DL1+ NK cells from Bw4+ donors and developed in B27 Tg+ mice (Bw4+ donors and Tg+ mice), while the least-responsive cells were KIR3DL1+ NK cells from Bw4− donors and developed in Tg− mice (Bw4− donors and Tg− mice). Recipients with the other two combinations (Bw4+ donors and Tg− mice and Bw4− donors and Tg+ mice) displayed a medium level of responsiveness. The stepwise escalation of NK cell responsiveness suggested that both the donor and recipient MHC environments are critical for the maintenance and adjustment of NK cell education (159).

Recently, the Nowak team proposed that inhibitory KIR (iKIR)-HLA pairs could predict the post-HSCT NK cell education status, i.e., donors presenting cognate HLA for donor iKIR and recipients lacking it predict a downward education level; in contrast, recipients presenting cognate HLA for donor iKIR and donors lacking it predict an upward education level. Those authors found that the decrease in iKIR–HLA pairs post-transplantation is associated with a higher relapse and poorer survival (160–162), indicating that reconstituted NK cells acquire better functions after interaction with more cognate HLA class I ligands in recipients. Zhao et al. also observed that, when the donors and recipients expressed three major HLA ligands (HLA-C1, C2, Bw4), patients with AML and myelodysplastic syndrome (MDS) experienced the lowest relapse rate, and NK cells expressing three inhibitory receptors exhibited the greatest cytotoxicity and cytokine responsiveness against K562 targets (163).

Based on the findings described above, it is likely that three factors (donor KIR, donor HLA, and recipient HLA) all
contribute to the variation in NK cell function. Therefore, the KIR ligand and receptor-ligand models, which only take two factors into account, may not accurately predict donors that exhibit the greatest NK cell function post-transplantation.

Factors That Affect NK Cell Reconstitution

Although CMV reactivation suggests an immune-compromised state, patients who experienced CMV reactivation had a lower relapse rate or better survival (70, 98, 99, 164). This protective effect might be attributed to the rapid maturation of NK cells. During CMV reactivation, NK cells that express NKG2C rapidly expand and continue to increase for 1 year (165). The number of CD56dim NK cells in the peripheral blood, their KIR expression, and IFN-γ production in response to K562 cells were also elevated in patients who developed CMV reactivation (165–173). Furthermore, nearly 60% of NKG2C+ NK cells achieved complete differentiation and expressed CD57 after CMV reactivation. These cells were termed memory-like NK cells and could be detected long after the primary CMV infection, offering a long-lasting protection (147, 166). In contrast, for non-CMV-infected patients, a higher proportion of NKG2A+ NKG2C− KIR− NK cells in the peripheral blood indicates a slow NK cell maturation. Interestingly, CMV antigen exposure to recipients also leads to an increased frequency of NKG2C+ NK cells, accompanied by increased KIR expression and decreased NKG2A expression (174).

As mentioned above, T cells in the graft impair the recovery of NK cells and KIR reconstitution (127–130). A possible explanation for this observation is that T cells compete with NK cells for IL-15, a cytokine that regulates immune cell survival and development (175, 176). Unlike ex-vivo TCD grafts, pre-transplant anti-thymocyte globulin (ATG) administration results in partial T cell depletion. Two recent studies found that ATG administration promoted NK cell recovery and delayed the reconstitution of CD4+ and CD8+ T cells, while sparing the effector memory T and regulatory T cells (Tregs) (177, 178). Compared with ATG, PT-Cy is more efficient in eliminating NK cells, with a higher residual ratio of CD4+ T cells and Tregs (179). Of note, several studies showed that T cells in the graft may contribute to a better NK cell function (153, 180). Several studies reported that CD56bright NK cells in lymph nodes could be stimulated by IL-2-producing T cells, resulting in NK cell maturation with higher IFN-γ secretion and cytotoxic functions (181, 182).

The relationship between GVHD and NK cell reconstitution remains controversial. Previous studies demonstrated that GVHD correlated with an impaired NK cell reconstitution and KIR expression (183–185). Ullrich et al. found that CD56bright NK cells were dramatically decreased in patients with GVHD, while CD56dim NK cells, the more mature subtype, did not show significant changes (185). In addition, Hu et al. found that the NKG2A subset of CD56dim NK cells was significantly decreased in patients with GVHD. Remarkably, a functional analysis showed that NKG2A+ NK cells from GVHD and non-GVHD patients exhibited a comparable GVL effect. Furthermore, the co-culture of donor T cells with NKG2A+ cells from non-GVHD patients suggested that NKG2A+ NK cells inhibit T cell proliferation and activation, indicating that the decreased number of NKG2A+ NK cells might be a cause, rather than a consequence, of GVHD (186). In addition, the administration of immunosuppressive agents could also affect immune recovery. Both Ullrich et al. and Giebel et al. suggested that steroid treatment, rather than GVHD, was related to the delayed NK cell reconstitution (184, 187).

FUTURE DIRECTIONS

Numerous studies have found that alloreactive NK cells affect treatment outcomes. Although great progress has been made through both pre-clinical and clinical investigations based on the three KIR models, the controversy remains, especially regarding the benefits of KIR alloreactivity on relapse control. Recent findings showed that donor KIR, donor HLA, and recipient HLA environment all contribute to the variation of NK cell function. The newly proposed iKIR-HLA pair model needs to be further examined in the future.

NK cells, the lymphocytes that are reconstituted first after transplantation, could be negatively affected by the T cells in the graft. However, NK cell function could also be promoted through T-cell-mediated activation. The exact interactions between NK and T cells, as well as the strategy to trigger a potential synergistic NK and T cell effect remains to be investigated.

It is noteworthy that the protective role of NK cell alloreactivity in relapse protection mostly exists in myeloid disease; in fact, some studies even found that NK cell alloreactivity increased the risk of relapse for patients with lymphoid disease. The discrepancy between expressing ligands among different diseases and their binding affinity to KIR should raise more attention. In this way, we might identify which patients would benefit from the KIR-based donor selection.

CONCLUSION

In the early period after transplantation, reconstituted alloreactive NK cell may not directly influence GVHD occurrence, as it is immature and it could be affected by T cells and immunosuppressive agents. The compatibility between donor KIR and the recipient HLA ligand may protect patients from infection. In the late period after transplantation, the iKIR-HLA pair model may reflect the variation in NK cell function, and quantitative analysis of KIR-HLA interactions may provide more convincing results regarding relapse and survival.

AUTHOR CONTRIBUTIONS

YZ and HH designed. FG and YY wrote this paper. All authors revised and approved the final manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (81670148 and 81730008) and Medical and Health Research Project of Zhejiang Province (2012KYB709).
REFERENCES

1. Gratwohl A, Brand R, Frassoni F, Rocha V, Niederwieser D, Reusser P, et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukemias: an EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Trans. (2005) 36:757–69. doi: 10.1038/sj.bmt.1705140

2. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, et al. Long-term survival and late deaths after allogeneic hematopoietic stem cell transplantation. J Clin Oncol. (2011) 29:2230–9. doi: 10.1200/JCO.2010.33.7212

3. Holmqvist AS, Chen Y, Wu J, Battles K, Bhatia R, Francisco L, et al. Assessment of late mortality risk after allogeneic blood or marrow transplantation performed in childhood. JAMA Oncol. (2018) 4:e182453. doi: 10.1001/jamaoncol.2018.2453

4. Styczynski J, Tridello G, Koster L, Jacobelli S, van Biezen A, van der Wef S, et al. Death after hematopoietic stem cell transplantation: changes over calendar year, infections, and associated factors. Bone Marrow Trans. (2020) 55:126–36. doi: 10.1111/s1440-1491-01624-z

5. Lanier LL, Le AM, Civin CI, Loken MR, Phillips JH. The relationship of CD16 (Leu-11) and Leu-19 (NKH-1) antigen expression on human peripheral blood NK cells and cytotoxic T lymphocytes. J Immunol. (1986) 136:4480-6.

6. Almeida-Oliveira A, Smith-Carvalho M, Porto LC, Cardoso-Oliveira J, Ribeiro Ados S, Falcao KR, et al. Age-related changes in natural killer cell receptors from childhood through old age. Hum Immunol. (2011) 72:319–29. doi: 10.1016/j.humimm.2011.01.009

7. Vivier E, Tomasello E, Baratin M, Walter T, Ugolini S. Functions of natural killer cells. Nat Immunol. (2008) 9:503–10. doi: 10.1186/nmi1582

8. Caligiuri MA. Human natural killer cells. Blood. (2008) 112:461–9. doi: 10.1182/blood-2007-09-077438

9. Lanier LL. NK cell receptors. Annu Rev Immunol. (1998) 16:359–93. doi: 10.1146/annurev.imag.16.1.359

10. Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, et al. Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. Annu Rev Immunol. (2001) 19:197–223. doi: 10.1146/annurev.immunol.19.1.197

11. Pugram HJ, Andrews DM, Smyth MJ, Darcy PK, Kershaw MH. Activating and inhibitory receptors of natural killer cells. Immunity. (2011) 36:2097–100. doi: 10.1016/j.immuni.2011.02.006

12. Wilson MJ, Torkar M, Trowsdale J. Genomic organization of a human killer cell inhibitory receptor gene. Tissue Antigens. (1997) 49:574–9. doi: 10.1111/j.1399-0039.1997.tb02804.x

13. Hsu KC, Chida S, Geraghty DE, Dupont B. The killer cell immunoglobulin-like receptor (KIR) genomic region: gene order, haplotypes and allelic polymorphism. Immunity. Rev. (2002) 190:40–52. doi: 10.1034/j.1600-656x.2002.19004.x

14. Parham P, Moffett A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. Nat Rev Immunol. (2013) 13:133–44. doi: 10.1038/nri3570

15. Manser AR, Weinhold S, Uhrberg M. Human KIR repertoires: shaped by genetic diversity and evolution. Immuno. Rev. (2015) 267:178–96. doi: 10.1111/imr.12316

16. Leung W. Use of NK cell activity in cure by transplant. Br J Haematol. (2011) 155:114–29. doi: 10.1111/j.1365-2457.2011.08823.x

17. Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song YJ, Yang L, et al. Licensing of natural killer cells by activating killer cell immunoglobulin-like receptors. J Immunol. (2005) 174:477–80. doi: 10.1182/blood-2004-10-2307

18. Alvarez M, Sun K, Murphy WJ. Mouse host unlicensed NK cells promote beta2-microglobulin-independent ligand on cancer cells. Immunity. (2017) 47:477–80. doi: 10.1016/j.immuni.2017.07.001

19. Seliger B, Ritz U, Ferone S. Molecular mechanisms of HLA class I antigen abnormalities following viral infection and transformation. Int J Cancer. (2006) 118:129–38. doi: 10.1002/ijc.21312

20. Pende D, Marcenaro S, Falco M, Martin S, Bernardo ME, Montagna D, et al. Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR and redefinition of inhibitory KIR specificity. Blood. (2009) 113:3119–29. doi: 10.1182/blood-2008-06-164103

21. Ognon J, Kralj Juric M, Ghimire S, Varanasi PR, Holler E, Greinix H, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. Front Immunol. (2016) 7:507. doi: 10.3389/fimmu.2016.00507

22. de Witte MA, Sarhan D, Davis Z, Felices M, Valler DA, Hinderlie P, et al. Assessment of late mortality risk after allogeneic blood or marrow transplantation performed in childhood. Blood. (2016) 127:2321–30. doi: 10.1182/blood-2015-08-665930
39. Leung W, Iyengar R, Turner V, Lang P, Bader P, Conn P, et al. Determinants of antileukemia effects of allogeneic NK cells. *J Immunol.* (2004) 172:644–50. doi: 10.4049/jimmunol.172.2.644
40. Cooley S, Trachtenberg E, Bergemann TL, Saeteurn K, Klein J, Le CT, et al. Donors with group B KIR haplotypes improve relapse-free survival after unrelated hematopoietic cell transplantation for acute myelogenous leukemia. *Blood.* (2009) 113:726–32. doi: 10.1182/blood-2008-07-171926
41. Davies SM, Ruggieri L, DeFor T, Wagner JE, Weisdorf DJ, Miller JS, et al. Evaluation of KIR ligand incompatibility in mismatched unrelated donor hematopoietic transplants. Killer immunoglobulin-like receptor. *Blood.* (2002) 100:3825–7. doi: 10.1182/blood-2002-04-1197
42. Giebel S, Locatelli F, Lamparelli T, Velardi A, Davies S, Frumento G, et al. Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors. *Blood.* (2003) 102:814–9. doi: 10.1182/blood-2003-01-0091
43. Schaffer M, Malmberg KJ, Ringden O, Ljunggren HG, Remmber M. Increased infection-related mortality in KIR-ligand-mismatched unrelated allogeneic hematopoietic stem-cell transplantation. *Transplantation.* (2004) 78:1081–5. doi: 10.1097/01.TP.00001370.19717.86
44. Elmaagacli AH, Ottinger H, Koldehoff R, Peceny R, Steckel NK, Treuschel R, et al. Reduced risk for molecular disease in patients with chronic myeloid leukemia after transplantation from a KIR-mismatched donor. *Transplantation.* (2005) 79:1741–7. doi: 10.1097/01.TP.0000164500.16053.C0
45. Yabe T, Matsuo K, Hirayasu K, Kashiwase K, Kawamura-Ishii S, Tanaka H, et al. Donor killer immunoglobulin-like receptor (KIR) genotype–patient cognate KIR ligand combination and antithymocyte globulin preadministration are critical factors in outcome of HLA-C-KIR ligand-mismatched T cell-replete unrelated bone marrow transplantation. *Blood Marrow Transplant.* (2008) 14:75–87. doi: 10.1016/j.bmt.2007.09.012
46. Verneris MR, Miller JS, Hsu KC, Wang T, Sees JA, Le CT, et al. Donor natural killer cell allorecognition of missing HLA haplotypes remains tolerant in HLA-matched sibling stem cell transplantation. *Blood.* (2019) 133:2305–10. doi: 10.1182/bloodadvances.2018012524
47. Zhu H, Bao X, Wu X, Wang M, Wu D, et al. Donor selection for KIR ligands and prediction of relapse after unrelated donor hematopoietic cell transplantation for hematologic malignancy. *Blood Marrow Transplant.* (2009) 44:97–103. doi: 10.1088/bmt.2008.432
48. Clausen J, Wolf D, Petzer AL, Gunsilius E, Schumacher P, Kircher B, et al. Impact of natural killer cell dose and donor killer-cell immunoglobulin-like receptor (KIR) genotype on outcome following human leukocyte antigen-identical haematopoietic stem cell transplantation. *Clin Exp Immunol.* (2007) 148:520–8. doi: 10.1111/j.1600-0625.2007.03360.x
49. Ludjakic J, Balavarca Y, Biceboller H, Rosenmayer A, Fae I, Fischer GF, et al. KIR genes and KIR ligands affect occurrence of acute GVHD after unrelated, 12/12 HLA matched, hematopoietic stem cell transplantation. *Bone Marrow Transplant.* (2009) 44:97–103. doi: 10.1038/bmt.2008.432
50. Clausen J, Kircher B, Auberg F, Schumacher P, Ulmer H, Hetzenauer G, et al. The role of missing killer cell immunoglobulin-like receptor ligands in T cell replete peripheral blood stem cell transplantation from HLA-identical siblings. *Blood Marrow Transplant.* (2010) 16:273–80. doi: 10.1038/j.10.2009.1021
51. Bjorklund AT, Schafer M, Fauriat C, Ringden O, Remmber M, Hammarstedt C, et al. NK cells expressing inhibitory KIR for non-self-ligands remain tolerant in HLA-matched sibling stem cell transplantation. *Blood.* (2010) 115:2686–94. doi: 10.1182/blood-2009-07-227940
52. Wu QQ, Zhao YM, Li X, Liu Y, Tan YM, Shi JM, et al. The beneficial impact of missing KIR ligands and absence of donor KIR2DS3 gene on outcome following unrelated hematopoietic SCT for myeloid leukemia in the Chinese population. *Bone Marrow Transplant.* (2010) 45:1514–21. doi: 10.1038/bmt.2010.3
53. Zhou H, Bao X, Wu X, Tang X, Wang M, Wu D, et al. Donor selection for KIR B haplotype of the centromeric motifs can improve the outcome after HLA-identical sibling hematopoetic stem cell transplantation. *Blood Marrow Transplant.* (2013) doi: 10.1016/j.bmt.2013.10.017
54. Sobekes RM, Wang T, Askar M, Gallagher MM, Haagensen M, Spellman S, et al. Impact of KIR and HLA genotypes on outcomes after reduced-intensity conditioning hematopoietic cell transplantation. *Blood Marrow Transplant.* (2015) 21:1589–96. doi: 10.1038/bmt.2015.05.002
55. Cook MA, Milligan DW, Fegan CD, Darbyshire PJ, Mahendra P, Clausen J, et al. Survival advantage with KIR ligand incompatibility in hematopoietic stem-cell transplantation. *Transplantation.* (2004) 78:1081–5. doi: 10.1097/01.TP.00001370.19717.86
clinical outcomes of allogeneic hematopoietic stem cell transplantation: Result of single center prospective study. *Hum Immunol.* (2015) 76:636–43. doi: 10.1016/j.jhimimm.2015.09.009

70. Cardozo DM, Marangon AV, da Silva RF, Aranha FJP, Visentainer JEL, Bonon SHA, et al. Synergistic effect of KIR ligands missing and cytomegalovirus reactivation in improving outcomes of haemopoietic stem cell transplantation from HLA-matched sibling donor for treatment of myeloid malignancies. *Hum Immunol.* (2016) 77:861–8. doi: 10.1016/j.jhimimm.2016.07.003

71. Faridi RM, Kemp TJ, Dharmani-Khan P, Lewis V, Tripathi G, Rajalingam R, et al. Donor-recipient matching for KIR genotypes reduces chronic GVHD and missing inhibitory KIR ligands protect against relapse after myeloablative, HLA matched hematopoietic cell transplantation. *PloS ONE.* (2016) 11:e0158242. doi: 10.1371/journal.pone.0158242

72. Neuchel C, Fuerst D, Niederwieser D, Bunjes D, Tsamadou C, Wulf G, et al. Impact of donor activating KIR genes on HSCT outcome in CI-ligand negative myeloid disease patients transplanted with unrelated donors-a retrospective study. *PloS ONE.* (2017) 12:e0196952. doi: 10.1371/journal.pone.0196952

73. Arima N, Kanda J, Tanaka J, Yabe T, Morishima Y, Kim SW, et al. Homozygous HLA-C1 is associated with reduced risk of relapse after HLA-matched transplantation in patients with myeloid leukemia. *Biol Blood Marrow Transplant.* (2018) 24:717–25. doi: 10.1016/j.bbmt.2017.11.029

74. Gaafar A, Sheereen A, Almoajib F, Eldali A, Chaudhri N, Mohamed SY, et al. Prognostic role of KIR genes and HLA-C after hematopoietic stem cell transplantation in a patient cohort with acute myeloid leukemia from a consanguineous community. *Bone Marrow Transplant.* (2018) 53:1170–9. doi: 10.1038/s41408-018-0123-7

75. Arima N, Kanda J, Yabe T, Morishima Y, Kako S, et al. Increased relapse risk of acute lymphoid leukemia in homozygous HLA-C1 patients after HLA-matched allogeneic transplantation: a Japanese national registry study. *Biol Blood Marrow Transplant.* (2020) 26:431–7. doi: 10.1016/j.bbmt.2019.10.032

76. Chen DF, Prasad VK, Broadwater G, Reinsmoen NL, DeOliveira A, Neuchel C, Furst D, Niederwieser D, Bunjes D, Tsamadou C, Furst D, Niederwieser D, Bunjes D, Tsamadou C, et al. Selecting the best donor for haploidentical transplant: The effect of single and combined activating killer immunoglobulin-like receptor genes on clinical outcome following T-cell-replete haploidentical hematopoietic cell transplantation. *Ann Hematol.* (2015) 94:2396–408. doi: 10.1007/s00277-015-2232-9.

77. Zhao XY, Chang YJ, Xu LP, Zhang XH, Liu KY, Li D, et al. HLA and KIR genotyping correlates with relapse after T-cell-replete haploidentical transplantation in chronic myeloid leukemia patients. *Br J Cancer.* (2014) 111:1080–8. doi: 10.1038/bjc.2014.223

78. Zhao XY, Chang YJ, Zhao XS, Xu LP, Zhang XH, Liu KY, et al. Recipient expression of ligands for donor inhibitory KIRs enhances NK cell function to control leukemic relapse after haploidentical transplantation. *Eur J Immunol.* (2015) 45:2396–408. doi: 10.1002/eji.201445057

79. Solomon SR, Aubrey MT, Zhang X, Piluso A, Freed BM, Brown S, et al. Selecting the best donor for haploidentical transplantation: impact of HLA, killer cell immunoglobulin-like receptor genotyping, and other clinical variables. *Biol Blood Marrow Transplant.* (2018) 24:789–98. doi: 10.1016/j.bbmt.2018.01.013

80. Willem C, Makanga DR, Guillaume T, Maniangou B, Legrand N, Gagne K, et al. Impact of KIR/HLA incompatibilities on NK cell reconstitution and clinical outcome after T cell-replete haploidentical hematopoietic stem cell transplantation with posttransplant cyclophosphamide. *J Immunol.* (2019) 202:2141–52. doi: 10.4049/jimmunol.1801489

81. Chen C, Busson M, Rocha V, Appert ML, Lepage V, Dulphy N, et al. Activating KIR genes are associated with CMV reactivation and survival after non-T-cell depleted HLA-identical sibling bone marrow transplantation for malignant disorders. *Bone Marrow Transplant.* (2006) 38:137–44. doi: 10.1038/sj.bmt.1705768

82. Schellekens J, Rozemuller EH, Petersen EJ, van den Tweel JG, Verdonck LF, Tilanus MG. Activating KIRs exert a crucial role on relapse and overall survival after HLA-identical sibling transplantation. *Mol Immunol.* (2008) 45:2255–61. doi: 10.1016/j.molimm.2007.11.014

83. van der Meer A, Schaap NP, Schattenberg AV, van Cranenbroek B, Tüsken HJ, Joosten I. KIR2DS5 is associated with leukemia free survival after HLA identical stem cell transplantation in chronic myeloid leukemia patients. *Mol Immunol.* (2008) 45:3631–8. doi: 10.1016/j.molimm.2008.04.016

84. Zaia JA, Sun YJ, Gallez-Hawkins GM, Thao L, Oki A, Lacey SE, et al. The effect of single and combined activating killer immunoglobulin-like receptor genotypes on cytomegalovirus infection and immunity after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* (2009) 15:315–25. doi: 10.1016/j.bbmt.2008.11.030

85. Bao XJ, Hou LH, Sun AN, Qiu QC, Yuan XN, Chen MH, et al. The impact of KIR2DS4 alleles and the expression of KIR in the development of acute GVHD after unrelated allogeneic hematopoietic SCT. *Bone Marrow Transplant.* (2010) 45:1435–41. doi: 10.1038/bmmt.2009.357

86. Venstrom JM, Gooley TA, Spellman S, Pring J, Malikki M, Dupont B, et al. Donor activating KIR3DS1 is associated with decreased acute GVHD in unrelated allogeneic hematopoietic stem cell transplantation. *Blood.* (2010) 115:3162–5. doi: 10.1182/blood-2009-08-236943

87. Tordai A, Bors A, Kiss KP, Balassa K, Andrikovics H, Batai I, et al. Donor KIR2DS1 reduces the risk of transplant related mortality in HLA-C2 positive young recipients with hematological malignancies undergoing reduced intensity transplantation with posttransplant cyclophosphamide. *Blood.* (2010) 115:3162–5. doi: 10.1182/blood-2009-08-236943
malignancies treated by myeloablative conditioning. PLoS ONE. (2019) 14:e0218945. doi: 10.1371/journal.pone.0218945

99. Nakamura R, Gendzekhadze K, Palmer J, Tsai NC, Mokhtari S, Forman SJ, et al. Influence of donor KIR genotypes on reduced relapse risk in acute myelogenous leukemia after hematopoietic stem cell transplantation in patients with CMV reactivation. Leukemia. (2019) 33:1559–69. doi: 10.1038/s41375-019-0704-1

100. Bultitude WP, Schellekens J, Szydlo RM, Anthias C, Cooley SA, Miller JS, et al. Presence of donor-encoded centromeric KIR B content increases the risk of infectious mortality in recipients of myeloablative, T-cell deplete, HLA-matched HCT to treat AML. Bone Marrow Transplant. (2020) 55:1847–55. doi: 10.1038/s41409-020-08588-9. [Epub ahead of print].

101. Weisdorf DJ, Cooley S, Wang T, Trachtenberg E, Vierra-Green C, Spellman S, et al. Improved survival with inhibitory killer immunoglobulin receptor (KIR) gene mismatches and KIR haplotype B donors after nonmyeloablative, HLA-haploidentical bone marrow transplantation. Biol Blood Marrow Transplant. (2010) 16:533–42. doi: 10.1016/j.bmt.2009.11.022

102. Oevermann L, Michaelis SU, Mezger M, Lang P, Toporski J, Berta ina A, et al. Presence of donor-encoded centromeric KIR B content increases the risk of infectious mortality in recipients of myeloablative, T-cell deplete, HLA-matched HCT to treat AML. Bone Marrow Transplant. (2020) 55:1847–55. doi: 10.1038/s41409-020-08588-9. [Epub ahead of print].

103. Symons HJ, Leffell MS, Rosser ND, Zahurak M, Jones RJ, Fuchs EJ. Improved survival with inhibitory killer immunoglobulin receptor (KIR) gene mismatches and KIR haplotype B donors after nonmyeloablative, HLA-haploidentical bone marrow transplantation. Biol Blood Marrow Transplant. (2010) 16:533–42. doi: 10.1016/j.bmt.2009.11.022

104. Perez-Martinez A, Ferreras C, Pascual A, Gonzalez-Vicent M, Alonso L, Badell I, et al. Haploidentical transplantation in high-risk pediatric leukemia: A retrospective comparative analysis on behalf of the Spanish working Group for bone marrow transplantation in children (GETMON) and the Spanish Grupo for hematopoietic transplantation (GETH). Am J Hematol. (2020) 95:28–37. doi: 10.1002/ajh.25661

105. Yu H, Tian Y, Wang Y, Mineishi S, Zhang Y. Dendritic cell regulation of graft-vs-host disease: immunostimulation and tolerance. Front Immunol. (2019) 10:3389. doi: 10.3389/fimmu.2019.00393

106. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukaemia reactions after bone marrow transplantation. Blood. (1990) 75:555-62. doi: 10.1182/bloodjournal735555

107. Marmont AM, Horowitz MM, Gale RP, Sobocinski K, Ash RC, van Bek kum AM. Antibodies to IFN-gamma prevent immunologically mediated acute graft-versus-host disease in F1 hybrid mice by pretreatment of the graft with anti-NK-1.1 and complement. Transplantation. (1992) 54:147–51. doi: 10.1097/00007890-199207000-00026

108. MacDonald GC, Gartner JG. Prevention of acute lethal graft-versus-host disease in F1 hybrid mice by pretreatment of the graft with anti-NK-1.1 and complement. Transplantation. (1992) 54:147–51. doi: 10.1097/00007890-199207000-00026

109. Pfeiffer MM, Feuchtinger T, Teltschik HM, Schumm M, Muller I, Handregtner R, et al. Reconstitution of natural killer cell receptors influences natural killer activity and relapse rate after haploidentical
transplantation of T- and B-cell depleted grafts in children. Haematologica. (2010) 95:1381–8. doi: 10.3324/haematol.2009.021211

130. Cooley S, McCullar V, Wangen R, Bergemann TL, Spellman S, Weisdorf DJ, et al. KIR reconstitution is altered by T cells in the graft and correlates with clinical outcomes after unrelated donor transplantation. Blood. (2005) 106:4370–6. doi: 10.1182/blood-2005-04-1644

131. Bjorkstrom NK, Beziat V, Cichocki E, Liu LL, Levine J, Larsson S, et al. CD8 T cells express randomly selected KIRs with distinct specificities compared with NK cells. Blood. (2012) 120:3455–65. doi: 10.1182/blood-2012-03-416867

132. van Bergen J, Thompson A, van der Slk A, Ottenhoff TH, Gussekloo J, Koning F. Phenotypic and functional characterization of CD4 T cells expressing Ig-like receptors. J Immunol. (2004) 173:6719–26. doi: 10.4049/jimmunol.173.11.6719

133. Lafarge X, Pitard V, Ravet S, Roumanes D, Hafary F, Dromer C, et al. Expression of MHC class I receptors confers functional intracellular heterogeneity to a reactive expansion of gammadeT T cells. Eur J Immunol. (2005) 35:1896–905. doi: 10.1002/eji.200425837

134. Pradier A, Papasarafim M, Li N, Rietveld A, Kaeest C, Gruaz L, et al. Small-molecule immunosuppressive drugs and therapeutic immunoglobulins differentially inhibit NK cell effector functions in vitro. Front Immunol. (2019) 10. doi: 10.3389/fimmu.2019.00556

135. Schmidt S, Schubert R, Demir A, Lehrnbecher T. Distinct effects of donor KIR genotype has a major influence on the rate of cytomegalovirus reactivation following T-cell replete stem cell transplantation. Blood. (2010) 117:2484–92. doi: 10.1182/blood-2010-10-316125

136. Wojtowicz A, Bochud PY. Risk stratification and immunogenic risk for infections following stem cell transplantation. Virulence. (2016) 7:917–29. doi: 10.1080/21505594.2016.1234566

137. Krieger E, Sabo R, Moezei S, Cain C, Roberts C, Kimball P, et al. Killer immunoglobulin-like receptor-ligand interactions predict clinical outcomes following unrelated donor transplantsations. Biol Blood Marrow Transplant. (2020) 26:672–82. doi: 10.1016/j.bbmt.2019.10.016

138. Montaldo E, Del Zotto G, Della Chiesa M, Mingari MC, Moretta A, De Maria A, et al. Human NK cell receptors/markers: a tool to analyze NK cell development, subsets and function. Cytometry A. (2013) 83:702–13. doi: 10.1002/cyto.a.22302

139. Scoville SD, Freud AG, Caligiuri MA. Modeling human natural killer cell development in the era of innate lymphoid cells. Front Immunol. (2017) 8:360. doi: 10.3389/fimmu.2017.00360

140. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. (2001) 22:633–40. doi: 10.1016/S1471-4906(01)02060-9

141. Gao et al. KIR and Transplant Outcomes
hematopoietic stem cell transplantation. *Blood Adv.* (2019) 3:4312–25. doi: 10.1182/bloodadvances.2019000242

164. Elmaagaci AH, Steckel NK, Koldehoff M, Hegerfeldt Y, Trenschel R, Ditschkowski M, et al. Early human cytomegalo virus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients. *Blood.* (2011) 118:1402–12. doi: 10.1182/blood-2010-08-304121

165. Della Chiesa M, Falco M, Podesta M, Locatelli F, Moretta L, Frassoni F, et al. Phenotypic and functional heterogeneity of human NK cells developing after umbilical cord blood transplantation: a role for human cytomegalovirus? *Blood.* (2012) 119:399–410. doi: 10.1182/blood-2011-10-386995

166. Foley B, Cooley S, Verneris MR, Pitt M, Curtisinger J, Luo X, et al. Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated NKG2C+ natural killer cells with potent function. *Blood.* (2012) 119:2665–74. doi: 10.1182/blood-2011-10-386995

167. Horowitz A, Guethlein LA, Nemat-Gorgani N, Norman PJ, Cooley S, Jin F, Lin H, Gao S, Wang H, Yan H, Guo J, et al. Characterization of IFN-gamma-producing natural killer cells induced by cytomegalovirus and with cytomegalovirus reactivation in the human KIR repertoire and involve activating KIRs. *Blood.* (2013) 121:2678–88. doi: 10.1182/blood-2012-10-459545

168. Jin F, Lin H, Gao S, Wang H, Yan H, Guo J, et al. Characterization of IFN-gamma-producing natural killer cells induced by cytomegalovirus reactivation after haploidentical hematopoietic stem cell transplantation. *Oncotarget.* (2017) 8:51–63. doi: 10.18632/oncotarget.13916

169. Bezat V, Liu LL, Malmberg JA, Ivarsson MA, Sohberg E, Bjorklund AT, et al. NK cell responses to cytomegalovirus infection lead to stable imprints in the human KIR repertoire and involve activating KIRs. *Blood.* (2013) 121:2708–16. doi: 10.1182/jimmunol.1301138

170. Charoudeh HN, Terszowski G, Czaja K, Gonzalez A, Schmitter K, Stern M. Modulation of the natural killer cell KIR repertoire by cytomegalovirus infection. *Eur J Immunol.* (2013) 43:480–7. doi: 10.1002/eji.20124389

171. Della Chiesa M, Falco M, Bertaina A, Muccio L, Alicata C, Frassoni F, et al. Human cytomegalovirus infection promotes rapid maturation of NK cells expressing activating killer Ig-like receptor in patients transplanted with NKG2C/- umbilical cord blood. *J Immunol.* (2014) 192:1471–9. doi: 10.4049/jimmunol.1302053

172. Muccio L, Bertaina A, Falco M, Pende D, Mezza R, Lopez-Botet M, et al. Analysis of memory-like natural killer cells in human cytomegalovirus-infected children undergoing alpha-beta-T and B cell-depleted hematopoietic stem cell transplantation for hematological malignancies. *Haematologica.* (2016) 101:371–81. doi: 10.3324/haematol.2015.134155

173. Davis ZB, Cooley SA, Cichocki E, Felices M, Wangen R, Luo X, et al. Adaptive natural killer cell and killer cell immunoglobulin-like receptor-expressing T cell responses are induced by cytomegalovirus and are associated with protection against cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation. *Blood Marrow Transplant.* (2015) 21:1653–62. doi: 10.1038/bmt.2015.05.025

174. Lodolce JP, Boone DL, Chai S, Swain RE, Dassopoulos T, Trettin S, et al. IL-15 receptor maintains lymphoid homeostasis by supporting lymphocyte homeing and proliferation. *Immunity.* (1998) 9:669–76. doi: 10.1016/S1074-7613(00)80664-0

175. Cooper MA, Bush JE, Fehniger TA, VanDeusen JR, Waite RE, Liu Y, et al. In vivo evidence for a dependence on interleukin 15 for survival of natural killer cells. *Blood.* (2002) 100:3633–8. doi: 10.1182/blood-2001-12-0293

176. Bosch M, Dhadda M, Hoegh-Petersen M, Liu Y, Hagel LM, Podgorny P, et al. Immune reconstitution after anti-thymocyte globulin-conditioned hematopoietic cell transplantation. *Cytotherapy.* (2012) 14:1258–75. doi: 10.3109/14653249.2012.715243

177. Servais S, Menten-Dedorajt C, Beguin Y, Seidel L, Goeth L, Daule C, et al. Impact of pre-transplant anti-T cell globulin (ATG) on immune recovery after myeloablative allogeneic peripheral blood stem cell transplantation. *PLoS ONE.* (2015) 10:e0130026. doi: 10.1371/journal.pone.0130026

178. Retiere C, Willem C, Guillaume T, Vie H, Gautreau-Rolland L, Scetet E, et al. Impact on early outcomes and immune reconstitution of high-dose post-transplant cyclophosphamide vs. anti-thymocyte globulin after reduced intensity conditioning peripheral blood stem cell allogeneic transplantation. *Oncotarget.* (2018) 9:11451–64. doi: 10.18632/oncotarget.24328

179. Nguyen S, Kuentz M, Vernant JP, Dhedin N, Bories D, Debre P, et al. Involvement of mature donor T cells in the NK cell reconstitution after haploidentical hematopoietic stem-cell transplantation. *Leukemia.* (2008) 22:344–52. doi: 10.1038/sj.leu.2405041

180. Fehniger TA, Cooper MA, Nuevo GJ, Cella M, Facchetti F, Colonna M, et al. CD56bright natural killer cells are present in human lymph nodes and are activated by T cell-derived IL-2: a potential new link between adaptive and innate immunity. *Blood.* (2003) 101:3052–7. doi: 10.1182/blood-2002-09-2876

181. Ferlazzo G, Thomas D, Lin SL, Goodman K, Morandi B, Muller WA, et al. The abundant NK cells in human secondary lymphoid tissues require activation to express killer Ig-like receptors and become cytotytic. *J Immunol.* (2004) 172:1455–62. doi: 10.4049/jimmunol.172.3.1455

182. Zhao XY, Huang XJ, Liu KY, Xu LP, Liu DH. Reconstitution of natural killer cell receptor repertoires after unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation: analyses of CD94/NKG2A and killer immunoglobulin-like receptor expression and their associations with clinical outcome. *Blood Marrow Transplant.* (2007) 13:734–44. doi: 10.1016/j.bmt.2007.02.010

183. Bunting MD, Varelias A, Souza-Fonseca-Guimaraes F, Schuster IS, Lineburg KE, Kuns RD, et al. GVHD prevents NK-cell-dependent leukemia and virus-specific innate immunity. *Blood.* (2017) 129:630–42. doi: 10.1182/blood-2016-08-734020

184. Ullrich E, Salzmann-Manrique E, Bakhitar S, Bremm M, Gerstner S, Herrmann E, et al. Relation between acute GVHD and NK cell subset reconstitution following allogeneic stem cell transplantation. *Front Immunol.* (2016) 7:595. doi: 10.3389/fimmu.2016.00595

185. Hu LJ, Zhao XY, Yu XX, Lv M, Han TT, Han W, et al. Quantity and quality reconstitution of NKG2A(+) natural killer cells are associated with graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* (2019) 25:1–11. doi: 10.1016/j.bbmt.2018.08.008

186. Giebel S, Driaæczkowska J, Czerw T, Wojnar J, Krawczyk-Kulis M, Nowak I, et al. Sequential recovery of NK cell receptor repertoire after allogeneic hematopoietic SCT. *Bone Marrow Transplant.* (2010) 45:1022–30. doi: 10.1038/bmt.2009.384

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Gao, Ye, Gao, Huang and Zhao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.