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How important is NK alloreactivity and KIR in allogeneic transplantation?

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Abstract

Relapse of acute myelogenous leukemia (AML) after allogeneic hematopoietic cell transplantation (allo HCT) is a major cause of death in transplant recipients. Efforts to control relapse by promoting donor T-cell alloreactivity, such as withdrawal of immune suppression or donor lymphocyte infusions, are limited by the propensity to induce graft versus host disease (GVHD) and by inadequate efficacy. Therefore, options for AML patients who have relapsed AML after allo HCT are few and outcomes are poor. Similar to T-cells, natural killer (NK) cells have potent anti-leukemia effector capacity, and yet unlike T-cells, NK cells do not mediate GVHD. Furthermore, their function does not require matching of human leukocyte antigens (HLA) between donor and recipient. Maximizing donor NK alloreactivity thus holds the exciting possibility to induce the graft versus leukemia (GVL) effect without engendering GVHD. Among the array of activating and inhibitory NK cell surface receptors, the killer Ig-like receptors (KIR) play a central role in modulating NK effector function. Here we will review how KIR mediates donor alloreactivity, discuss the role of KIR gene and allele typing to optimize allo HCT donor selection, and discuss how KIR may aid adoptive NK and other cell therapies.

Keywords

acute myelogenous leukemia; allogeneic hematopoietic cell transplantation; allo HCT; alloreactivity; AML; graft versus host disease; GVHD; graft versus leukemia; GVL; killer Ig-like receptors; KIR; natural killer; NK

Introduction

Allogeneic hematopoietic cell transplantation (allo HCT) is an effective curative therapy for AML. The benefit of allo HCT relies on a well-recognized graft versus leukemia effect,

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whereby donor lymphocytes eradicate malignant cells and allow for long-term disease-free survival [1,2]. T-cell mediated GVL relies on recognition of disparities in major and minor histocompatibility antigens that are not restricted to leukemic blasts, opening the possibility of widespread injury to normal tissues in the form of GVHD. In contrast, NK cells are innate immune cells that recover quickly after allo HCT and confer significant effector function against malignant and virally infected target cells [3–7]. NK cells do not contribute to GVHD, even in an HLA-mismatched environment [8–11]. Thus, NK cells represent an attractive option to boost the antileukemia properties of allo HCT without increasing transplant related toxicities.

Several activating and inhibitory cell surface receptors collectively influence NK effector function, including the natural cytotoxicity receptors, NKG2 receptors, and KIR. During NK development, interaction of inhibitory KIR with their cognate ligands within specific class 1 HLA epitopes induces tolerance to target cells [12]. For example, KIR2DL1 recognizes HLA-C alleles characterized by Asn^{77} and Lys^{80} (HLA-C2 group); KIR2DL2/3 recognizes HLA-C alleles characterized by Ser^{77} and Asn^{80} (HLA-C1 group); and KIR3DL1 recognizes HLA-A and -B alleles with the Bw4 epitope [13]. Engagement of inhibitory KIR with self-HLA educates, or “licenses,” NK cells for effector function [14,15]. Target cells lacking the self-class I HLA ligand, such as during viral infection or malignant transformation, become sensitive to cytotoxicity from licensed NK cells, whose recognition of “missing self” in the target cell results in reactivity. In individuals who lack cognate class 1 HLA ligands for their inhibitory KIR, NK cells expressing inhibitory KIR for non-self HLA are termed “unlicensed” and exhibit decreased effector capacity. This mechanism limits autoreactivity in resting conditions; however, unlicensed NK cells can gain higher levels of effector function when stimulated by cytokines or by CD16 engagement and can exert significant GVL in an inflammatory milieu such as the post transplantation environment [16–19].

Optimizing KIR/HLA interactions: Missing self and missing ligand

The importance of KIR-mediated donor NK alloreactivity was first described in HLA-mismatched allo HCT, where licensed NK reactivity due to “missing self” could be tested. AML patients lacking KIR ligands (HLA-C1, -C2, or -Bw4) present in their haploidentical donors (“missing self”) experienced lower rates of relapse and higher survival [20,21]. More recently, several groups demonstrated that in an HLA-matched (and thus KIR ligand-matched) allo HCT recipients that lacked KIR ligands experienced less relapse and improved survival [19,22,23]. Together, these results indicate that licensed NK cells mediate GVL in a KIR ligand-mismatched environment, and unlicensed NK cells mediate GVL in KIR ligand-matched scenarios when KIR ligands are absent in the recipient (“missing ligand”). A major limitation to the application of these findings is that HLA is germline encoded and fixed in the recipient, ensuring that if all KIR ligands are expressed, engagement of donor inhibitory KIR is unavoidable. In order to circumvent this problem, more recent innovations exploit the significant genetic variation within KIR to select donors based on variations in the *degree* of inhibitory or activating signals delivered between donor KIR genes and leukemic HLA. This advent allows for KIR based donor optimization even in the setting where missing ligand or missing self are not achieved.

Genetic diversity in KIR

In contrast to HLA, the KIR genetic region varies in gene content between individuals, with individual haplotypes containing between 9 and 15 individual KIR genes (Table 1) [24–26]. KIR gene clusters are organized into two haplotype groups, including haplotype-A that contains predominantly inhibitory KIR, and haplotype-B, whose members are more diverse with greater variability in activating KIR [26]. The A and B haplotypes occur in roughly equal frequency in European populations; therefore approximately one-third of donors will lack the activating rich haplotype B [27,28]. Cooley and others analyzed the role of donor KIR haplotype B content in preventing relapse in 448 recipients of allo HCT for AML and found a significant improvement in survival in recipients of donors with at least one haplotype B compared to recipients of haplotype A/A donors (31% (95% confidence interval: 26–36%) versus 20% (13–27%), $P = 0.007$) [28]. Fifty-five percent of patients in this cohort underwent HLA-mismatched transplant and peripheral blood grafts were used in 11%. The benefit seemed to be related to specific gene motifs noted in the centromeric portion distinctive of B-haplotypes (cenB), with homozygosity for cenB found to be particularly favorable. In a follow-up report of an expanded cohort of 1,532 donor/recipient pairs this group demonstrated that the benefit of centromeric haplotype-B donors was restricted to recipients of HLA class I mismatched allo HCT[29]. It should be noted that in an analysis of 1,277 separate individuals, we did not find a difference in relapse in recipients with a donor homozygous for the activating KIR- rich centromeric portion of haplotype B (cenBB) versus those with either cenAB or cenAA donors (28.1% versus 33.7%, HR = 0.77 (0.52–1.13), $P = 0.18$) [30].

It is possible that all activating KIR are not equally relevant to leukemia control. In vitro studies demonstrated a potent reactivity of NK cells that express the activating receptor KIR2DS1, particularly against an HLA-C2 expressing target cell [31]. Enhanced function due to KIR2DS1-mediated reactivity, however, is diminished if the NK cell is educated high levels of its ligand HLA-C2, such as occurs in HLA-C2 homozygous individuals [32]. We subsequently tested the hypothesis that KIR2DS1$^+$ donors who did not express a high background of HLA-C2 (HLA-C1/x) would result in a lower incidence of relapse in a cohort of 1,277 allo HCT recipients with AML in comparison to those donors whose KIR2DS1+ NK cells may be educated in an HLA-C2 homozygous environment [30]. Reflecting the higher and lower function of KIR2DS1$^+$ NK cells observed in vitro in HLA-C1/x versus HLA-C2 homozygous individuals, the incidence of relapse in recipients with HLA-C1/x, KIR2DS1$^+$ donors was 24.9% compared to 32.3% in those with KIR2DS1$^-$ donors and 37.3% in those with HLA-C2 homozygous donors ($P = 0.003$ and $P = 0.09$, respectively). Importantly, there was not an increased incidence of acute GVHD in recipients of KIR2DS1$^+$ donor allo HCT. The protective findings of KIR2DS1 and HLA-C1 were subsequently confirmed in an independent analysis on a largely non-overlapping cohort of AML patients [29].

It remains an open question what are the relative roles of the various activating KIR. Incomplete information with respect to the respective ligands for all activating KIR hampers a rigorous evaluation of these receptors. Currently, the majority of investigations address the role of activating KIR in disease control and focus on limited and well described activating

KIR and their respective ligands; however, activating KIR may play a role in preventing infectious complications of allo HCT or reducing the incidence of GVHD [33,34]. The biological mechanism underlying the latter phenomenon is not well understood.

Allotype variation in inhibitory KIR and transplantation outcomes

Beyond diversity in KIR gene representation, individual KIR genes have considerable allelic polymorphism. Among inhibitory KIR, KIR3DL1 exhibits the greatest degree of diversity, with approximately 80 alleles described to date. [Immuno Polymorphism Database, http://www.ebi.ac.uk/ipd/kir/). The KIR3DL1 alleles may be characterized by expression density into four main groups: Highly expressed KIR3DL1 (KIR3DL1-high) alleles such as *001 and *002, poorly expressed KIR3DL1-low alleles such as *005 and *007, KIR3DL1-null alleles such as *004 that are not expressed on the cell surface, and KIR3DS1 that does not interact with HLA-Bw4 [35]. We found that KIR3DL1-high and KIR3DL1-low groups confer stereotyped inhibitory signal strength when encountering specific HLA-Bw alleles [36]. For example, KIR3DL1-high alleles interact with HLA-Bw4 with isoleucine at position 80 (Bw4-I^{80}) to confer a high inhibition signal but will interact with HLA-Bw4 with threonine at position 80 (HLA-Bw4-T^{80}) to confer a weak inhibition signal. It is thought that KIR3DL1-low allele groups interact inversely, conferring high inhibition upon engagement with Bw4-T^{80} and low inhibition upon engagement with Bw4-I^{80}. Thus, allele typing of both recipient HLA-Bw and donor KIR3DL1 may predict the degree of inhibition imparted to donor NK cells in vivo. The biological relevance of KIR3DL1/HLA-Bw4 was first described in persons infected with HIV, where specific interactions predictive for a high degree of NK education and response capacity protected patients from progression to AIDS [37]. We have demonstrated that strong interactions produce higher response capacity [36], and we hypothesize that these same strong interactions may also predict for easier inhibition. In collaboration with the National Marrow Donor Program (NMDP) and Center for International Blood & Marrow Transplant Research (CIBMTR), which provided sequencing -based donor KIR allele typing, we completed a pilot study of donor KIR3DL1-Bw4 allele combinations for 299 AML patients undergoing HCT from largely HLA-matched unrelated donors [38]. Here, donors with presumed low or no inhibition KIR3DL1-Bw4 allele combinations were associated with significantly lower relapse and higher survival following HCT, and the highly licensed, but presumed highly “inhibitable” combinations were associated with higher relapse (HR = 0.24, $P = 0.0002$). Importantly, there was no association with relapse protection when considering donor KIR3DL1 allele independent of HLA. These data are consistent with our model that HLA expression on tumor cells leads to inhibition of licensed NK cells, an outcome avoided by unlicensed NK cells (recipient Bw6/Bw6) and NK cells with poor or no KIR3DL1/HLA-Bw4 interaction. Mechanistic studies definitively demonstrating hierarchical inhibitory properties between the KIR3DL1 and HLA-B allele combinations are still needed.

In order to further evaluate the role of KIR3DL1 allotypes in transplant for AML, we devised and validated an intermediate resolution SSP based KIR3DL1 typing method representing 97.5% of alleles found in the general population [35]. We are currently evaluating the role of KIR3DL1 allotypes using this method in an expanded cohort of individuals via collaboration with the NMDP and CIBMTR. Interestingly, in a separate

study of pediatric solid tumor patients, we find an association between high inhibition KIR3DL1 and HLA-B allele pairs and poor outcome when compared to low inhibition KIR3DL1 and HLA-B allele pairs [39]. This finding supports the impact of the KIR3DL1-expressing population in vivo, its role in tumor clearance, and the prospect of titrating NK response based on KIR3DL1 and HLA-B allotype interaction.

Beyond KIR3DL1, it is likely that allelic polymorphism within other inhibitory KIR genes influence the donor NK activation state. Bari and colleagues demonstrated that KIR2DL1 with arginine at position 245 (R^{245}) conferred greater inhibition upon HLA-C2 ligand engagement when compared to cysteine (C^{245}), likely due to faster internalization of the latter receptor [40,41]. Using a different typing method, the investigators subsequently evaluated the impact of donor KIR2DL1 dimorphism at amino acid position 245 in 313 pediatric allo HCT recipients with hematologic and solid tumors [41]. Surprisingly, they found that recipients of allografts from a KIR2DL1-R^{245+} donor were protected from relapse and had improved overall survival when compared to donors who were homozygous for KIR2DL1-C^{245}. It should be noted that less than 10% of donors were found to be homozygous for KIR2DL1-C^{245}, somewhat limiting the applicability of these results.

Intrigued by these contradictory in vitro and clinical findings, we have independently evaluated the impact of KIR2DL1-R^{245} vs -C^{245} in a homogeneous cohort of >1,200 adult patients undergoing 9/10 or 10/10-HLA matched unrelated donor allo HCT for AML. In contrast to the findings in the pediatric allo HCT study and in keeping with a model of protective effects for the less inhibited KIR allotypes, we observed that transplant recipients of stem cell allografts from donors exclusively with KIR2DL1-C^{245} alleles were more protected from relapse when compared to recipients of donors exhibiting one or more KIR2DL1-R^{245} alleles (unpublished data). Whether KIR2DL1 allotypes are protective for relapse in specific biological subsets of leukemia found in greater frequencies in pediatric patients, or whether differences in transplant patterns between the two groups influenced the disparate outcomes is unknown and warrants further investigation. Undoubtedly, improved allele typing methods will aid future genetic association studies [42].

KIR2DL2/3 also exhibits allelic polymorphism, although the role of this genetic variation in determining transplant outcomes is not described [43]. It is expected that there will be some impact of receptor diversity, given a recent report that dimorphism at amino acid position 35 governs greater NK education and enhanced cytotoxic capacity [44]. When interpreting genetic association studies, it is important to be aware that several KIR alleles between different KIR loci exist in strong positive linkage disequilibrium with each other. This has been best described for the centromeric haplotype, where specific alleles for KIR2DL1 are known to be closely associated with KIR2DL2, −2DS2, and −2DL3 respectively [45,46]. Careful attention to these genetic relationships will avoid over-interpretation and assignment of primacy one polymorphic KIR site over another.

KIR in HLA-mismatched allogeneic hematopoietic cell transplantation

A recent resurgence in the use of haploidentical HLA matched donors, along with continued widespread use of umbilical cord blood (UCB) allografts, has renewed interest in exploring

the role of donor KIR genotypes after HLA mismatched transplantation. Early reports of the role of KIR in UCB allo HCT are conflicting. We found no evidence for examination of KIR genotyping in single UCB allo HCT in 83 patients examined at our center. Brunstein and colleagues found evidence of increased GVHD and greater risk of death in recipients of UCB allo HCT with reduced intensity conditioning who were KIR ligand mismatched [47]. Nevertheless, Sekine and others found, using a receptor-ligand model considering specific KIR gene and ligand interactions that increased NK alloreactivity resulted in lower relapse and increased survival in 110 recipients of UCB allo HCT [48]. Investigations of the role of specific KIR allele typing in UCB allo HCT are limited by the smaller numbers of UCB transplants performed at most centers and are thus not well investigated.

Early reports of KIR in haploidentical allo HCT conducted by Ruggeri and colleagues focused mainly on haploidentical transplantation using ex vivo T-cell depletion [21]. More recent reports continue to describe a positive association with activating KIR genes after T-cell deplete haploidentical transplantation [34]. Recent interest in the use of post-transplant cyclophosphamide created a relative vacuum in our understanding of the role of donor KIR in this transplant platform, as the role of donor KIR genotypes with this platform are not well described. Oevermann and colleagues recently observed an association between use of donors with the activating KIR-rich haplotype B and a reduction in relapse of pediatric acute lymphoblastic leukemia [49]. However, in a small series of patients Galaverna and colleagues found no association with KIR haplotype B content and outcomes [50]. Large-scale studies examining the role of haploidentical donor KIR gene and allele typing will likely come as the biospecimen repositories of haploidentical transplants grow worldwide.

The role of KIR in emerging therapies

Due to initial reports indicating the sensitivity of AML to NK alloreactivity [20,23], the investigation of KIR genotyping in allo HCT has largely been concentrated on patients with AML. Nevertheless, NK cells may play a role in control of non-myeloid malignancies and may be effective outside of the realm of traditional allo HCT. Multiple studies now define adoptive NK cell therapies as safe, albeit with modest efficacy [51,52]. KIR genotyping and examination of patient KIR ligand expression should play a role in this emerging field. Other areas of future interest include, in particular, examination of the role of NK alloreactivity in controlling antibody dependent cellular cytotoxicity. For example, Du and colleagues demonstrated that rituximab therapy can overcome the inhibitory signal in unlicensed NK cells after autologous transplantation for follicular lymphoma, and that missing KIR ligand may play a role in this population [53]. This concept widens the scope of relevance for NK cells to a variety of non-AML malignancies and in a variety of clinical settings. Recent publications outlining the role of KIR geno- and allotyping in antibody therapy for neuroblastoma are proof-of-principle that this avenue of investigation is likely to yield further discoveries [39].

Conclusions

Taken together, these results indicate that donor KIR geno- and allotypes influence the degree of NK education and inhibition when taken into consideration with donor and

recipient HLA. Practically speaking, the most current and relevant application of this technology is in patients undergoing unrelated donor allo HCT for AML, where the likelihood of selection of a donor among multiple available donors allows for the use of KIR-based donor evaluation. Multiple prospective studies are currently evaluating whether prospective unrelated donor selection is feasible and results in improved outcomes for AML patients undergoing allo HCT. Beyond this, further exploration of the role of inhibitory KIR allotypes in determining transplant outcomes will refine our understanding of what makes a "good KIR donor" in the future. It is likely that the next decade will lead to considerable refinement in our understanding of KIR in allo HCT. Finally, the role of NK cells in promoting antibody-dependent cellular cytotoxicity is not well understood and could lead to considerable improvements in the efficacy of monoclonal antibodies.

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Table 1

Major Inhibitory and Activating KIR Genes

Killer Ig Receptor	Ligand	Comments	Selected references
Inhibitory			
KIR2DL1	HLA-C2	Dimorphism at position 245 influences binding capacity to HLA-C2	[40]
KIR2DL2/3	HLA-C1	Dimorphism at position 35 influences binding capacity to HLA-C1	[43,44]
KIR2DL4	HLA-G	Both activating and inhibitory	[54]
KIR2DL5	Unknown		
KIR3DL1	HLA-Bw4	Allelic polymorphism influences binding capacity to Bw4	[36]
KIR3DL2	HLA-A*3, -A*11, -B*27	Potential therapeutic target in cutaneous T-cell lymphoma	[55]
KIR3DL3	Unknown		
Activating			
KIR2DS1	HLA-C2	KIR2DS1^{+} NK cells are hypofunctional when derived from C2/C2 donors.	[30,32]
KIR2DS2	HLA-A*11	Associated with decreased CMV after solid organ allograft	[56]
KIR2DS3	Unknown		
KIR2DS4	HLA-A*11		
KIR2DS5	Unknown		
KIR3DS1	Unknown	Segregates as allele of KIR3DL1, associated with decreased TRM	[33]