

Killer Immunoglobulin like Receptor and Hematopoietic Stem Cell Transplantation: A Brief Review

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Abstract

Hematopoietic stem cell transplantation is a cure for various leukemic patients, and is based on the requirement of finding a full Human leukocyte antigen (HLA) matched donor. The shortage of HLA matched donors has given rise to HLA mismatched transplants in recent years due to the ease of finding more than one donor within the family. However, there could still be complications due to the HLA disparity, which has been reduced due to modifications in transplant protocols such as using post-transplant cyclophosphamide resulting in favorable outcomes. Recently, the role of non-HLA genes on affecting HSCT outcomes has been highlighted. The influence of Killer Immunoglobulin like receptor (KIR) genes and their cognate HLA ligand match/mismatch on better transplant outcomes has become prominent recently. Various studies have highlighted positive, negative and neutral impact of these interactions. This review aims to discuss the different NK cell alloreactivity models, the interaction of KIR receptor ligands and its effects on hematopoietic stem cell transplant outcomes as postulated by previous research groups. Herein, the necessity of KIR genotyping and knowing KIR receptor-ligand match/mismatch in order to predict better transplant outcomes is also highlighted.

Keywords: Killer-immunoglobulin like receptor; hematopoietic stem cell transplantation; NK cell alloreactivity

Introduction

Hematopoietic stem cells (HSCs) are immature blood cells in the bone marrow which can evolve and differentiate into all other type of blood cells. This property of HSCs is used to overcome a functional deficit in leukemic patients by hematopoietic stem cell transplantation (HSCT) [1]. The potential of allogeneic HSCT in curing a variety of hemato-lymphoid malignancies such as acute myeloid/lymphoid leukemia (AML/ALL), chronic myeloid/lymphoid leukemia (CML/CLL), and myelodysplastic syndrome (MDS) among others has been established [2].

The selection of a donor for HSCT is based on HLA matching between the patient and donor. The frequency of finding a HLA matched related donor is about 25 percent [3]. For 75% of the patients, who do not have a HLA matched related donor, the options of matched unrelated donor (MUD), matched cord blood or a haploidentical related transplantation exists. Due to ergonomic constraints, most patients opt for haploidentical related transplantation. The advantage of using a haploidentical donor is immediate availability of related donor which means shorter time to transplant [4]. However, increased HLA disparity between patient and donor has been associated with higher graft versus host disease (GvHD) and poor overall survival (OS) [5]. This disadvantage has been taken care of by using post-transplant cyclophosphamide in haploidentical transplants which has resulted in similar transplant outcomes as with HLA matched related and HLA matched unrelated transplants [6-11].

It has been observed that even after finding a HLA matched donor the success of HSCT is limited due to conditions such as GvHD and relapse, which highlights the role of non-HLA genes in predicting transplant outcomes. One such gene is the KIR gene present on Natural Killer (NK) cells, which has recently been implicated in post-transplant outcomes [12-16].

Killer Immunoglobulin like Receptor Genes

The main function of NK cells is cytotoxicity of virally infected or transformed cells and hence they play an important role in innate

immunity [7]. NK cell functions are modulated by various surface receptors. One such receptor is the Killer immunoglobulin like receptor (KIR). Both NK cells as well as a subset of T cells carry the KIR glycoproteins [18]. The KIR gene is mapped to chromosome 19q13.4 and includes a total of 15 KIR genes (KIR 2DL1, 2DL2, 2DL3, 2DL4, 2DL5A, 2DL5B, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1), and 2 pseudogenes (2DP1, 3DP1) [19].

KIRs can be inhibitory or activating depending on the length of its intra-cytoplasmic tail: inhibitory KIRs are denoted as DL because of the presence of a long intra-cytoplasmic tail and activating KIRs are denoted as DS because of the presence of a short intracytoplasmic tail [20]. The inhibitory KIR has an immunoreceptor tyrosine based inhibitory motif (ITIM) which carries out the inhibitory function via tyrosine phosphatases. The activating KIR on the other hand carries the immunoreceptor tyrosine based activating motif (ITAM) and is responsible for the activating function via the DAP12 transmembrane signaling adaptor protein [21]. The KIR gene content differs in individuals due to its highly polymorphic nature (haplotypic as well as allele level). Hence, the chance of 2 individuals with identical KIR is less than 0.01 percent [22]. Depending on the KIR gene content, an individual can have either a KIR A or a KIR B haplotype. The KIR A haplotype includes the inhibitory genes KIR3DL1, KIR3DL2, KIR3DL3, KIR2DL1, KIR2DL3, KIR2DL4, and only one activating gene KIR2DS4, whereas, the KIR B haplotype has a mixed gene content with combinations of the inhibitory genes KIR3DL2, KIR3DL3, KIR2DL1, KIR2DL2, KIR2DL4, KIR2DL5A, KIR2DL5B, and activating genes

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KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, KIR3DS1. Since, the KIR A haplotype has only one activating gene, it is referred to as the more inhibitory haplotype, whereas, the KIR B haplotype with more than one activating genes is referred to as the more activating haplotype [23,24]. Due to the presence of multiple activating genes, the KIR B haplotype is considered to have a greater cytolytic potential as compared to KIR A haplotype [22].

HLA

The ligands for KIRs are the HLA A, B and C molecules. The gene encoding HLA is the most polymorphic and is encoded by chromosome 6. HLA molecules are present on almost every nucleated body cell. HLA has a major role in eliciting an immune response by either presenting variable peptides or by recognizing polymorphic fragments on non-self HLA molecules. Due to this property of recognizing self and non-self, HLA molecules have been associated with graft failure, graft versus host disease (GvHD) and mortality post hematopoietic stem cell transplantation [25].

KIR HLA interaction

KIR (Chr 19) and HLA (Chr 6) are encoded by different chromosomes and hence segregate independently. This indicates that in any individual, there could be KIR receptor present but not its cognate HLA ligand. Alloreactivity of NK cells is caused when the target cells lack the HLA ligands (HLA C1, HLA C2 and HLA Bw4) for the inhibitory KIR receptors present in the graft. This situation is common when there is a viral infection or in the case of malignancy. Virally infected or transformed cells lose their self-HLA class I ligands

due to which they will be recognized as foreign by licensed NK cells and are in turn lysed. This phenomenon of missing ligand was explained by Ruggeri et al. [16] in their ligand incompatibility model (2002).

There could be 2 different KIR HLA C ligands differentiated on the basis of the amino acid present at position 80 of the alpha-1 domain. C1 which includes the HLA-C*01/*03/*07/*08/*12/*14/ and *16 alleles has the amino acid asparagine, whereas, the C2 which includes the HLA-C*02/*04/*05/*06/*15/*17/*18 alleles has the amino acid lysine [26]. The HLA B has two different motifs the Bw4, which includes the alleles B*05, B*51, B*13, B*17, etc., and Bw6 which includes the alleles B*07, B*08, B*14, B*18, B*22 etc. Bw4 motif carries either a threonine (Bw4-80T) or isoleucine (Bw4-80I) at position 80 and is a ligand for KIR3DL1. The Bw6 motif however is not a ligand for KIR. When the inhibitory KIR receptors bind to their cognate HLA ligand (KIR2DL1-HLAC2, KIR2DL2-HLAC1, KIR2DL3-HLAC1, KIR3DL1-HLABw4), they cause inhibition of cytotoxicity, likewise, when activating KIR receptors bind to their cognate HLA ligand (KIR2DS2-HLAC1, KIR2DS1-HLAC2) or when there is an inhibitory KIR receptor ligand mismatch it results in enhanced cell lysis [27,28] Figure 1 will have two parts C1 negative C2 negative (present here) and then explain the hypothesis based on the figures. If the host carries the HLA C1,C2 and HLA Bw4 epitopes for which the corresponding inhibitory receptor KIR2DL2/3,KIR2DL1 and KIR3DL1 is present in the donor, there will be inhibition of donor NK cell activity because of the inhibitory receptor-ligand match (Figure 1A). However, in case the host does not carry the cognate inhibitory ligand for donor inhibitory KIR receptor KIR2DL1 or KIR2DL2/3 there will be no inhibition leading

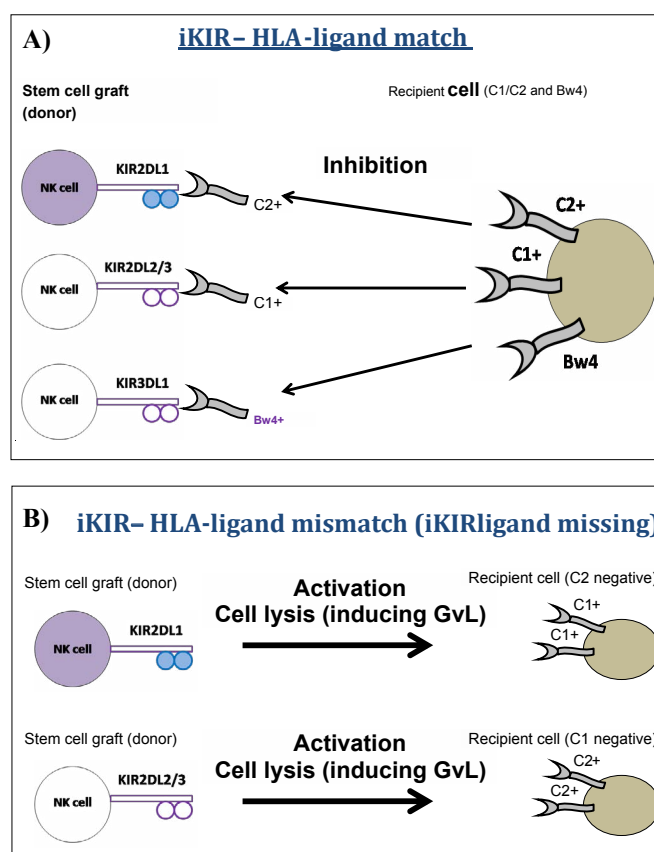


Figure 1: Interaction of inhibitory KIR receptors with their cognate ligand resulting in A) inhibition or B) activation of cytotoxicity.

to enhanced donor NK cell activity and a good graft versus leukemic response (Figure 1B).

KIR alloreactivity models

The HLA-KIR alloreactivity has been explained by the 4 KIR alloreactivity models by Beksac and Dalva [29]:

- Missing ligand model
- KIR ligand-ligand model
- KIR receptor-ligand model
- KIR haplotype model

Missing ligand model

Beksac and Dalva [29], first highlighted the impact of HLA KIR ligands and the missing ligand model in allogeneic HSCT. This model suggest that when there is a lack of HLA ligands in the host for the inhibitory KIRs present in the donor, it will lead to increased alloreactivity which will kill the leukemic cells and results in better transplant outcomes. Wu et al. [30] reported lower relapse risk in leukemic patients missing KIR ligands undergoing unrelated HSCT. Hsu et al. [31], observed in their study on HLA mismatched unrelated donor HSCT that absence of HLA C2 or HLA Bw4 ligands in the host was associated with lower hazards of relapse. Wang et al. [32], reported higher OS and DFS in myeloid patients who were C1/C2 homozygotes as compared to C1C2 heterozygotes.

KIR ligand-ligand model

This model is based on the assumption that whenever the HLA KIR ligands carried by the donor and the patient are different, there will be alloreactivity against the non-self-cell. There are various contradictory data for this model. Ruggeri et al. [16], conducted a haploidentical transplant study in AML cases, wherein, KIR ligand-ligand mismatch in graft versus host (GvH) direction contributed to alloreactivity and hence protected from relapse and GVHD. Giebel et al. [33], conducted a study in unrelated HLA matched and mismatched HSCT using Anti thymocyte globulin as GVHD prophylaxis. Their results suggest that patients with KIR ligand incompatibility with their donors had better OS and DFS. Duan et al. [34] reported that in haploidentical HSCT, there was better disease free survival (DFS) in patients who had mismatched HLA C ligands with their donors. Similarly, lower risk of GvHD, better OS and DFS has been reported for HLA matched HSCT, wherein, patients were mismatched for HLA C ligands with their donors [31]. Recently, a few T cell replete haploidentical HSCT studies have shown favourable outcomes such as better OS and DFS in KIR ligand- ligand mismatch transplants, wherein post transplant cyclophosphamide was used for GvHD prophylaxis [34,35].

The above studies highlight the importance of KIR ligand ligand mismatch for better transplant outcomes, however, few other studies report no difference in transplant outcomes based on patient-donor KIR ligand ligand mismatch in both HLA matched /mismatched related and unrelated HSCTs [36-38].

Some researchers have also indicated higher TRM and acute GvHD and lower DFS and OS in KIR ligand mismatched HSCTs [39-41]. A study conducted by De Santis et al. [42], have also reported increased probability of graft rejection when the KIR ligand-ligand mismatch is in the Graft versus Host direction.

KIR receptor-ligand model

According to this model, there will be higher NK cell alloreactivity when there is a mismatch between the inhibitory KIR receptor and its cognate HLA ligand.

A recently conducted haploidentical HSCT study on leukemic patients reported that whenever there was an inhibitory receptor missing in the donor for the HLA C ligand present in the host, there was better 2 year OS and relapse free survival [42]. Similarly, Solomon et al. [44] reported in their study on T cell replete haploidentical HSCT with post-transplant cyclophosphamide that whenever there were KIR receptor ligand mismatches among the patient and donor, it led to better transplant outcomes. Contradictory to these findings, Shimoni et al. [45], reported worst transplant outcomes in KIR mismatched patient-donor pairs. Torio et al. [46] reported higher chronic GvHD in patients who were KIR ligand mismatched with their donors. The explanation to this phenomenon is that whenever, there is an inhibitory KIR receptor ligand mismatch, there will be loss of inhibition and hence higher NK cell activity. If the mis-match is in the graft versus host (GvH) direction, it lead to loss of inhibition of donor NK cell activity which results in enhanced removal of leukemic cells leading to better graft versus leukemia (GvL) effect. However, if the inhibitor KIR receptor HLA ligand mis-match is in the host versus graft (HvG) direction, there will be no inhibition of host NK cell cytolytic activity towards the graft and hence there is a greater chance of graft rejection due to the graft being recognized as foreign. This results in higher probability of relapse and hence poor transplant outcomes.

KIR haplotype model

The KIR B haplotype has more number of activating genes and hence transplantation from donor carrying the B/X haplotype has been linked to favorable transplant outcomes. Recent studies have reported significantly better OS in patients undergoing T cell replete matched unrelated HSCT, when the donor carries the KIR B/X haplotype as compared to donors with the A/A haplotype [16,46-48], reported a 30% improvement in RFS in AML cases undergoing HLA matched/mismatched T cell replete unrelated donor HSCT when the donor had the KIR B/X haplotype as compared to when the donor carried the A/A haplotype.

Contradictory reports from Kroger et al. [40] suggest that in T cell replete haplotransplants involving post-transplant cyclophosphamide, lower non relapse mortality, better OS and event free survival was seen in patients with donors carrying the A/A haplotype as compared to donors with B/X haplotype. Torio et al. [46] reported higher chronic GvHD in patients who were transplanted with a donor who carried a KIR B/X haplotype. Similarly, Hosokai et al. [49] reported higher risk of acute GvHD in patient who received transplants from donors carrying the KIR B/X haplotype.

Conclusion

Our group conducted a study on 41 T cell replete post Cy haploidentical transplantation cases, wherein, we found that KIR ligand ligand mismatch between the patient donor pairs, patients carrying the C1C1 HLA C ligand and missing the Bw4 ligand, or inhibitory KIR receptor ligand mismatches in the GvH direction led to better OS and RFS (unpublished data). Results from different groups for the KIR models are contradictory based on the type of patients, source of stem cell used, conditioning regimen and GvHD prophylaxis used (Table 1).

Reference	Type of Transplant	Diagnosis	Cohort Size (N)	Results
Hsu et al. [21]	T cell replete HSCT, HLA matched/mismatched unrelated donors	Hematological malignancies	1770	A lower relapse rate was reported in HLA mismatched patients homozygous for HLA B or HLA C epitopes (p=0.004).
Cooley et al. [25]	T cell replete HLA matched/ mismatched unrelated HSCT	Acute myeloid leukemia	209 HLA matched; 239 HLA mismatched	Donor with KIR B/X genotype led to better 3-year OS (p=0.007). B/X donors resulted in higher incidence of cGvHD (p=0.03). B/X donors showed lowerRR as compared to AA donors (p=0.002)
De Santis et al. [42]	HLA Mismatched unrelated donor	Hematological malignancies	104	KIR ligand mismatch between patient donor pairs resulted in higher TRM and lower DFS and higher risk of graft rejection. KIR ligand mismatch in GvH direction led to higher prevalence of Grade III-IV aGvHD
Wang et al. [32]	HLA matched sibling donor	Hematological malignancies	52	Incidence of cGvHD was lower in C1 and C2 homozygotes as compared to C1C2 heterozygotes (p = < 0.005). Higher OS and DFS in C1 and C2 homozygotes as compared to C1C2 heterozygotes (p=0.034 and 0.024 respectively)
Giebel et al. [33]	T cell depleted haploidentical unrelated donors	Hematological malignancies	130	Patients with KIR ligand incompatibility with their donors had better OS (p=0.006) and DFS (p=0.0007)
Farag et al. [37]	Unrelated HSCT (T cell replete/deplete)	Hematological malignancies	1571	No difference in TRM, aGvHD, cGvHD, relapse and DFS was observed in KIR ligand matched/ mismatched cohort
Kroger et al. [40]	T cell depleted unrelated	Hematological malignancies	142	KIR ligand mismatch resulted in higher TRM (p=0.03), reduced OS (p=0.02) and DFS (p=0.03). Donors with KIR AA haplotype resulted in reduced RR (p=0.003) and improved DFS (p=0.04)
Bao et al. [47]	T cell depleted unrelated	Hematological malignancies	75	Donors with KIR A/A haplotype and 2DS4*001 allele resulted in higher risk of aGvHD (p=0.010)
Weisdorf et al. [39]	T cell depleted mismatched unrelated	Advanced Myeloid malignancy	24	No difference in aGvHD, cGvHD, relapse was observed in KIR matched and KIR mismatched cohort
Sivula et al. [38]	Unrelated HSCT	Hematological malignancies	186	No difference in transplant related outcomes in KIR ligand matched and KIR ligand mismatched cohort
Wu et al. [30]	Unrelated HSCT	Hematological malignancies	116	Patients with missing KIR ligand for receptor present in donor showed decreased RR (p=0.019). In myeloid group, missing KIR ligands also improved 5 year OS (p=0.034) and DFS (p=0.024). Donor activating KIR2DS3 gene results in increased RR (p=0.003), decreased OS (p= 0.04) and DFS (p=0.003).
Duan et al. [34]	Haploidentical HSCT	Hematological malignancies	74	HLA C ligand mismatch resulted in better DFS (p=0.024).
Symons et al. [17]	Haploidentical (bone marrow source)	Hematological malignancies	86	iKIR gene-gene mismatched patient donor pairs resulted in improved OS (p=0.0003), DFS (p=0.01) and RR (p=0.025) Donors with KIR B/X genotype and patient with AA genotype improved OS (p=0.004), DFS (p=0.05), and NRM (p=0.046)
Zhang et al. [43]	Haploidentical HSCT	Hematological malignancies	47	Donors with matched inhibitory KIR receptors with patient C1/C2 ligand resulted in better 2 year OS and lower RR as compared to mismatched group (p=0.03 and p=0.05 respectively)
Bastos et al. [35]	T cell replete post Cy haploidentical HSCT	Hodgkins Lymphoma	33	iKIR gene-gene mismatch and KIR ligand mismatch between patient donor pairs resulted in better OS
Wanquet et al. [36]	T cell replete post Cy haploidentical HSCT	Hematological malignancies	144	KIR ligand mismatch between patient donor pairs resulted in lower RR (p=0.013), Better DFS (p=0.028)
Solomon et al. [44]	T cell replete haploidentical	Hematological malignancies	208	KIR receptor-ligand mismatch in GvH direction resulted in reduced RR/ progression. Donor with KIR BX genotype and KIR2DS2 better OS
Torio et al. [46]	T cell replete haploidentical	Hematological malignancies	30	KIR receptor ligand matches in GvH direction resulted in lower cGvHD (p=0.004). Donor with KIR B/X haplotype resulted in lower cGvHD (p=0.033)
Shimoni et al. [45]	T cell replete haploidentical post Cy	Acute lymphoid/ myeloid leukemia	444	KIR ligand mismatching resulted in worse survival (p=0.03)
Hosokai et al. [49]	T cell replete haploidentical	Hematological malignancies	304	Donor KIR B/X, higher risk of grade III to IV aGvHD (p=0.02)

Table 1: Results of different studies on the effect of KIR in HSCT.

However, these studies suggest that screening for the KIR genotype and KIR ligand match/mismatch may implicate transplant outcomes and should be routinely used in selecting a suitable donor for hematopoietic stem cell transplantation.

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