Review Article

Roadmap to KIR Mismatching Model and its Impacts on HSCT Outcome

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Abstract: Purpose of the review: In recent years we have been able to see the different Killer cell immunoglobulin like receptor (KIR) mismatching model with corresponding to their receptors and their ligands. Starting from the ligand-ligand mismatch to the KIR genes tools to know more about how the mismatching works and to discover more about how their mismatching can be benefited in the Hematopoietic Stem Cell Transplant (HSCT) outcome. This review serves the purpose of knowing their limitation and benefit after KIR Mismatching and how every model served their purpose and how they lead to the development and discovery of new model and their role as a better and worse outcome in HSCT, and what the future opportunity holds for these KIR . In this review we will learn about KIR and HSCT, how they help in selection of donor on the basis of KIR mismatching and how they impact on HSCT outcome. *Recent findings:* Most of the researches and study have shifted themselves towards learning about KIR genes and how it benefits in HSCT. *Summary:* Current and past researches have shown beneficial role of KIR mismatching and their role in HSCT outcome.

Keywords: Alloreactivity of Natural Killer cells; Graft versus Leukemia; Hematopoietic Stem Cell Transplantation; KIR mismatching model.

INTRODUCTION

NK receptors can be divided into two families; C -type lectin-like family and immunoglobulin superfamily, including killer immunoglobulin-like receptor(KIR), Leukocyte Immunoglobulin like Receptor(LILR) and natural cytotoxic receptor(NCR)[1]. The genes encoding the KIR receptor (chromosome 19) and the Human Leukocyte Antigen (HLA) class I ligand (chromosome 6) are located on different chromosomes. This allows for different KIR-HLA interactions in different individuals, allowing for genetic diversity of the immune response. Therefore, certain KIR-HLA combinations are associated with various autoimmune diseases, viral infections and cancer [2, 3].

Selection of the Donor on the basis of Human Leukocyte Antigen (HLA) compatibility is the most important but Age, Sex, parity, Cytomegalovirus Serostatus, ABO blood type and Cell dose also plays an important role in HSCT outcome [4]. Donor selection on the basis of these criteria has long being in practiced and many institutions have adapted to KIR genotyping and KIR ligand status for finding the donor on the basis of KIR mismatching.

KIR mismatching

Many researches were conducted using different model of KIR mismatching, among them the most popular are ligand-ligand mismatch, receptor-ligand mismatch and receptor-receptor mismatch. Until now, there are three model of KIR mismatching that has been proposed, they are Perugia KIR ligand model(Ligand-ligand mismatch: ligand present in donor that the recipient lack)[5], the Memphis receptor-ligand model (Receptor-ligand mismatch: receptor of the ligand present in donor that the recipient lack)[6], Receptor-receptor mismatch(receptor present in donor that the recipient lack)[7], it is considered the prototype of Stanford group 'KIR haplotype model' [8, 9].

Ligand-Ligand Mismatch Model

As for the ligand-ligand mismatch model [5], 112 high-risk acute leukemia patients received hematopoietic stem cell transplants from HLA haplotype–mismatched family donors, among them 57 were AML and 35 were ALL, Ruggeri *et al*. [5] compared

between two groups who were Non-alloreactive NK cells and alloreactive NK cells and the group with NK alloreactivity had a better outcome for AML, results for ALL was not significant. HLA antigens are transplantation antigens involved in the interaction between patient and donor lymphocytes. Therefore, for successful transplantation, it is best to use the HLA identical donor for transplantation. Unlike B and T cells allo- recognition involves the recognition of foreign HLA antigens, NK cell Allogeneic Recognition primarily involves the identification of missing self- HLA antigens. KIR ligand incompatibility refers to the presence or absence of a specific HLA ligand (in a patient) for a particular inhibitory KIR receptor (in a donor). NK cells binds potential target cells on the basis of activating and inhibitory receptors. If the target cell does not inhibit the ligand associated with binding to the inhibitory receptor of NK cells, the NK cell lysis occurs[10]. NK allogeneic reactions may be involved in the outcome of HSCT.

Receptor-Ligand Mismatch Model

Receptor-Ligand Mismatch, Leung et al.[6] found that ligand-ligand mismatch model did not give the better outcome for lymphoblastic group, they suggested there was more to this than just ligand-ligand mismatch, so they proposed the receptor-ligand model. They took 36 patients and checked the outcome for three model (Cytotoxicity, ligand-ligand mismatch and receptor-ligand mismatch model). They found that the receptor-ligand better predicted leukemia relapse and anti-leukemic effect were greater in group with receptor-ligand mismatch. This study showed that even the patient who were ligand-ligand match but were receptor-ligand mismatch, had outcome better predicted with receptor-ligand mismatch model. Although the ligand to activating KIR are still not well known, so interaction between inhibitory KIR and HLA class I molecules determines the alloreactivity of NK cells. KIR2DL2 and KIR2DL3 recognize HLA-C group 1 (C1) -associated alleles, which are characterized by asparagine residues at position 80 of a-1 helix (HLA-CAsn80), and KIR2DL1 recognition of HLA-C group 2 (C2). The allele is characterized by a lysine residue of 80 (HLA-C Lys80), KIR3DL1 recognizes the HLA-Bw4 allele, and KIR3DL2 recognizes the HLA-A3 / A11 allele [11]. Patients were classified under receptor-ligand mismatch if the patient is not expressing the ligands for the donors KIR. HLA class I subgroups ligands were (1) HLA-A3 Or -A11, (2) HLA-Bw4; or (3) HLA-Cw group (C1 or C2)[12].

Receptor-Receptor Mismatch Model

As for the Gangne et al. [7] receptor-receptor mismatch, the study showed that HLA C mismatch and having a activating receptor in the donor that the recipient lacked led to aGvHD, donor having 2DS3 was related with aGvHD. Donor and Recipients KIR Gene Matching is defined as the donor and recipient having the same KIR genotype. Donor and recipient KIR genes mismatch is defined as KIR gene not present in the recipient is found in the donor KIR genes, and vice versa.

KIR Haplotype Model

Stanford Haplotype model [8], showed that Haplotype B missing in donor and present in recipient had the best survival, less relapse and aGvHD.2DS3 was a protective factor for cGvHD. As we can see that 2DS3 was related with aGvHD in Gangne et al. receptor-receptor mismatch model but same 2DS3 was found to be protective against cGvHD in McQueen et al. Haplotype model. Group A haplotype defined as a combination of nine Genes: KIR 3DL3, 2DL3, 2DP1, 2DL1, 3DP1, 2DL4, 3DL1, 2DS4 and 3DL2. Detection of at least one gene for KIR B haplotypes defined locus (KIR 2DL5,2DS1,2DS2,2DS3,2DS5 or 3DS1) were classified as group B Haplotype[13]. Individuals with only group a genes were designated as A/A genotypes. Having one gene for B and one for A (A / B heterozygous), or only B genes (B / B homozygous). B haplotype individuals is designated as B / x. [14]. Further subdivision of a haplotype into subgroups as A-1 and A-2. A-1 is defined as carrying a full-length 2DS4 haplotype A, while A-2 is defined as a haplotype carrying a deleted 1D variant. The combination of A-1 and A-2 can be divided into AA-1. AA-2 and AA-3. For group B, there are 15 different haplotypes named B1 to B15 depending on their frequency. The combination of genes in group A and B1 / B2 haplotypes is the most common genotype, named Bx1 and Bx2[13,14]. KIR Haplotype model focuses more on KIR activators in HSCT.

The donor Centromeric (Cen) and Telomeric (Tel) KIR haplotype model

Genotypes for the Cen and Tel portions of the KIR locus was determined by the presence or absence of one or more B haplotypes defining KIR genes. Cen-A01 (cA) contains the gene combinations of 3DL3, 2DL3, 2DP1, 2DL1 and 3DP1, while Tel-A01 (tA) contains the gene combinations of 2DL4, 3DL1, 2DS4 and 3DL2. The haplotype consists of cA-tA. Cen-B01 and Cen-B02 are alternative centromere motifs of the common B KIR haplotype, which contain 3DL3, 2DS2, 2DL2 and 3DP1 (Cen-B01) or 3DL3, 2DS2, 2DL2, 2DL5B, 2DS3, 2DP1, 2DL1 and 3DP1 (Cen-B02) in the centromere region. Cen-B01 and Cen-B02 are shortened to cB. In the combination of 2DL4, 3DS1, 2DL5A, 2DS3/S5, 2DS1 and 3DL2 telomere regions are the most common haplotype B- specific telomere segments, defined as Tel-B01 (tB). B haplotype consists of following centromic and telomeric combinations: cB-tA, cB-tB and cA-tB[13].

Focus of Research towards KIR2DS2 and KIR2DS1

As researches pointed out towards the role of HLA-C1 recognizing centromeric genes(KIR2DL2/L3/S2) being dominated in NK alloreactivity as they are higher in number and predominantly regenerating from CD34+ cells after transplant[15,16] researches diverted towards finding the roles of 2DS2.We know little about 2DS2 binding to HLA-C1,research show that 2DS1 binds to HLA-C2,some evidences show that 2DS2 binds to tumor cell ligand like beta2-Microglobulin-independent tumor cell ligand[17], which raises the hope of its use in selection of donor. Knowing about activating KIR and their binding to some of the tumor cell ligand can open a new way in the future for adoptive NK cell therapy.

Researches on KIR mismatching and HSCT outcome

Many researches and study done for KIR mismatching had led to better survival outcome and disease protection and same KIR mismatching had led to worst survival outcome and disease protection. There is more to KIR mismatching and many things are still unfolding, it creates confusion among researcher and practitioner whether to follow one or to ignore other. Going through many researches and studying them, method they use or Chemotherapeutic agents they use have impacted the outcome. There is no strict protocol or methods for KIR mismatching, and it's confusing when you read the literature as one shows benefit and other shows disadvantages of KIR mismatching. For the past decades, researcher have shown a keen interest in the KIR mismatching as this might open a new door for proper management of patients going through HSCT. New researches are coming, new methods are applied, goal is the same to find a better donor and enhance the better HSCT outcome. Table 1. shows the researches of KIR mismatching model in HSCT.

Table-1: KIR mismatching model and their HSCT outcome

KIR mismatching model	References	Number of Transplants	Disease	Treatment	HSCT outcome
Ligand-Ligand Mismatch Model					
	Davies et al. [18]	175	Myeloid, lymphoid	Unrelated Donor	Worse
	Lowe et al. [19]	88	Myeloid, lymphoid	Unrelated Donor	Worse
	Giebel et al. [20]	130	Myeloid, lymphoid	Unrelated Donor	Better
	Bishara et al. [21]	62	Myeloid, lymphoid	Haploidentical HSCT	Worse
	Farag et al. [22]	1571	Myeloid	Unrelated Donor	Worse
	Ruggeri et al. [23]	112	Myeloid	Haploidentical HSCT	Better
	Huang et al. [24]	116	Myeloid, lymphoid	Haploidentical HSCT	Worse
	Yabe et al. [25]	1489	Myeloid, lymphoid	Unrelated Donor	Worse
	Willemze et al. [26]	218 single unit CB	Myeloid, lymphoid	Cord Blood	Better
	Brunstein et al. [27]	102 single CB	Myeloid, lymphoid	Cord Blood	Worse
Receptor-Ligand Mismatch Model					
	Leung et al. [28]	51	Myeloid, lymphoid	Haploidentical HSCT	Better
	Wanqu et al. al.[29]	144	Myeloid, lymphoid	Haploidentical HSCT, post-transplant Cyclophosphomide	Better
Receptor-Receptor Mismatch Model					
	McQueen et al. [8]	59	Myeloid	Activating KIR in HSCT,MSD, All activators	Worse

KIR, killer immunoglobulin like receptor; HSCT, hematopoietic stem cell transplant; MSD, matched sibling donor

Two studies have specifically demonstrated inconsistencies in the results of studies related to NK allogeneic responses. Davies et al.[18] studied 175 pediatric and adult patients with different malignancies who underwent transplantation of at least one HLA allele mismatch. The results showed that KIR ligand-incompatible grafts had a poor survival rate and had no significant effect on relapse rate. The two biggest factors affecting survival are relapse and GvHD. Anti-Thymocyte Globulin(ATG) was used for T cell depletion. The result was supported by Schaffer et al. [30] who also reported a decrease in survival rate and had no effect on relapse rate. Contrary to these studies, Giebel et al.[20] studied 121 pediatric and adult patients with different malignancies and without ATG. The results reported an increase in the survival rate with KIR ligand incompatibility. Giebel's Research supports Ruggeri et al.[5] in which increased survival and reduced relapse rates were found for ligand-ligand incompatibility. It was suggested that harmful and beneficial effects of KIR ligand incompatibility of the study resulted from the use of ATG, because more T cells were depleted [30].

When donor T cells interact with the receptor of Antigen presenting Cells (APC), GvHD occurs. In mouse models, NK cells have been shown to destroy APC, prevents T cell activation and prevents GvHD [5]. Morishima et al.[31] studied 1790 patients who underwent the T cells replete Graft transplantation, he found that KIR ligands incompatibility in patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia(CML) lead to grade III-IV GvHD and mortality increased. But, with the use of anti- Thymocyte Globulin (ATG) prevented GvHD even with KIR ligand incompatibility. KIR ligand Mismatch impacts on GvHD may be harmful or beneficial depending on the presence of donor T cells. Other study has also presented similar observations [32].

A beneficial effect on relapse rate was observed when investigating KIR ligand incompatibility associated with relapse. Giebel et al.[20] studied 130 unrelated patients - donor transplant, he reported a link between KIR ligand incompatibility and reduced relapse rates. For Myeloid leukemia group, the effect was more prominent than lymphoid leukemia. So, myeloid malignancies respond more strongly to ligand incompatibility. However, it has been reported that NK cell-mediated effects have an effect on childhood ALL [33]. In childhood leukemia blast cells express high levels of adhesion molecules, which contribute to NK cell-mediated target cell lysis [34]. Unfortunately, in the study by Giebel et al. [20] ALL patients were not classified as children or adults. A study by Hsu et al.[35] also supports Giebel et al.[20], in which he pointed out that patients with AML , CML and ALL had a reduced risk of relapse in the absence of certain KIR ligands. There is evidence to support NK cell-mediated Graft versus Leukemia on ALL patients, but is more prominent in AML patients[26].

KIR Repertoire for HSCT results regarding the increase in specific KIR- activated receptors in donors increases or decreases relapse and GvHD rate[36-38] Recent researches are more focused on KIR repertoire (specific KIR genomes in individuals) and its impacts on survival, GvHD and relapse rates. Research by Kroger *et al.* [36] and Cooley *et al.* [39] shows very different results. Kroger *et al.* [36] studied 142 patients with leukemia receiving unrelated stem cell transplantation and ATG were used for T cell depletion. The results showed that KIR haplotype B / x donor significantly reduced the survival rate of transplanted patients, having KIR haplotype A / A survival rate is higher. Giebel *et al.*[20] found similar observations as Kroger *et al.* [36] showing worse outcome. Contrary to the study by Kroger *et al.* [36] Cooley *et al.* [39] studied 448 patients; the results showed that donor KIR haplotype A/A had more treatment-related mortality than donors with B/x haplotypes. Cooley *et al.*[39] continued to study KIR haplotypes of HLA- matched unrelated HSCT results in patients receiving T cell-replete grafts. The survival rate of homozygous haplotype B (B / B) donors or at least heterozygous haplotype B (B / x) donors was significantly higher than that of A/A donors. A donor with at least one B motifs showed a 30 % increase in relapse-free survival compared to a homozygous haplotype A donor (A / A). Cooley *et al.*[39] study also showed an increase in chronic GVHD rates in patients transplanted with KIR haplotype B/x or B/B donors but not acute GvHD .

Kroger *et al.* [36] hypothesized that the relapse rate were associated with activating receptors and relapse increased with having activating receptors. These observations by Kroger *et al.* [36] were also supported by Schaffer *et al.* [30] Cooley *et al.* [39] reported that donor KIR haplotype A/A had a higher relapse rate than the B/x haplotype .The conflicting results may be related to the method used for transplantation, thereby affecting whether the matching of the donor KIR genotype is beneficial or detrimental.

In a recent study of 1446 patients there was a poor outcome with presence of activating KIR,200 patients with C2 homozygotes had inferior OS, DFS and relapse but C2 homozygotes with KIR2DS2+ donor had better OS and DFS[40]. In haplo-identical setting also having KIR2DS1 or/and KIR3DS1 lead to decrease in non-relapse mortality and increase in event free survival [41]. As for the case of Myelodysplastic syndrome Haplotype A had a higher risk of converting to AML compared to Haplotype B [42]. Table 2. shows the activating KIR in HSCT and their outcome.

Table-2: Activating KIR in HSCT and their outcome

KIR mismatching model	References	Number of Transplants	Disease	Treatment	HSCT outcome
KIR Haplotype Model					
	Verheyden *et al.* [37]	65	Myeloid, lymphoid	Activating KIR in HSCT,MSD, 2DS1 and 2DS2	Better
	Kroger *et al.* [36]	142	Myeloid, lymphoid	Activating KIR in HSCT,URD, All activators	Worse
	Giebel *et al.* [43]	25	Myeloid, lymphoid	Activating KIR in HSCT,URD, 2DS1 and 2DS2	Worse
	Kim *et al.* [44]	53	Myeloid	Activating KIR in HSCT,MSD, 2DS1	Better
	Triplett *et al.* [45]	59	Myeloid, lymphoid	Activating KIR in HSCT,URD, 2DS1	Worse
	Pende *et al.* [33]	21	Myeloid, lymphoid	Activating KIR in HSCT with Ligand-Ligand Mismatch, Haploidentical donor,2DS1	Better
	Ludajic *et al.* [46]	124	Myeloid, lymphoid	Activating KIR in HSCT, URD, 2DS2	Better
	Cooley *et al.* [39]	448	Myeloid	Activating KIR in HSCT,URD, All activators	Better
	Venstrom *et al.* [47]	1087	Myeloid, lymphoid	Activating KIR in HSCT, URD, 3DS1	Better
	Stringaris *et al.* [42]	68	Myeloid	Activating KIR in HSCT,MSD, 2DS1 and 3DS1	Better
	Cooley *et al.* [15]	1086	Myeloid	Activating KIR in HSCT, URD, Cen B	Better
	Venstrom *et al.* [15]	1277	Myeloid	Activating KIR in HSCT, URD,2DS1 and 3DS1	Better
	Cooley *et al.*[14]	1532	Myeloid	Activating KIR in HSCT, URD,KIR B/x	Better
	Oevermann *et al.* [49]	85	Lymphoid	Activating KIR in HSCT, Haploidentical donor, KIR B/x	Better
	Mancusi *et al.*[41]	161	Myeloid, lymphoid	Activating KIR in HSCT with Ligand-Ligand Mismatch, Haploidentical donor,2DS1 and 3DS1	Better
	Sobecks *et al.*[50]	909	Myeloid	Activating KIR in HSCT,URD, 2DS1	Worse
	Sekine *et al.*[51]	206	Myeloid, lymphoid	Activating KIR in HSCT,CB, 2DS1 and 2DS2	Better
	Neuchel *et al.*[40]	1446	Myeloid, lymphoid	Activating KIR in HSCT,URD, 2DS1 and 2DS2	Better
	Elfishawi *et al.*[52]	65	Myeloid, lymphoid	Activating KIR in HSCT,MSD,2DS3	Better
	Hosokai *et al.*[53]	61	Myeloid, lymphoid	Activating KIR in HSCT,KIR B/x	Worse
	Burek Kamenaric *et al.* [54]	111	Myeloid, lymphoid	Activating KIR in HSCT,2DS4	Worse
	Torio *et al.*[55]	30	Myeloid, lymphoid	Activating KIR in HSCT with Ligand-Ligand Mismatch, Haploidentical donor, KIR B/x	Better

KIR, killer immunoglobulin like receptor; HSCT, hematopoietic stem cell transplant; MSD, matched sibling donor; URD, Unrelated donor; CB, cord blood; KIR B/x, Donor KIR genotype B/x

KIR Haplotype Frequencies

Mostly in northeast Asians Haplotype A is more commonly seen than haplotype B but in population like Indian, Australian, American and most of Caucasian population's haplotypes A and B have a more even distribution?[56-59]. In Southern Han population of China, the ratio of haplotype A vs. B is about 3:1 (74.8% vs. 25.2%)[60] which is similar to previous studies conducted in Han populations from Zhejiang and Taiwan[61], Many of the studies that were conducted for KIR mismatching for HSCT outcome includes the Caucasian group of population where Haplotype B is more commonly seen or Haplotype A or Haplotype B is evenly distributed. Results may vary according to materials and methods that were used like KIR mismatching model, regimens used, mode of transplants, methods of donor selection and severity of the diseases.

KIR related strategies

In a study of 21 patients with myeloid malignancy, patients were infused with haplo-identical IL-2 NK cells before transplantation showed positive results with survival, goal was to increase anti-leukemic effect without worsening GvHD[62]. In another study 26 pediatric patients relapse/refractory leukemia were KIR mismatched with their NK donors and 2/3 had a good response and proceeded to HSCT [63]. All of these studies were done in haplo-identical donor setting, by KIR mismatching we might be able to avoid the entire poor HSCT outcome that arises from HLA mismatch. NK cells role is not just limited to HSCT outcome, researches have shown NK cell infiltrates solid tumors, its efficacy against intracranial neoplasms, gastric carcinoma and squamous cell carcinoma of the lung [64-66]. Anti KIR antibodies has also been successfully used for AML, Lymphoma and Multiple Myeloma, it has shown preclinical efficacy for these diseases and more clinical trials are going on for its efficacy and safety [67-70].

CONCLUSION

Past and current researches have seen a great possibility of KIR mismatching and their benefit in HSCT outcome, whether it's ligand-ligand mismatch model, receptor-ligand mismatch model and KIR Haplotype model. All model has their benefits and their shortcomings whether it's due to the methods, materials or due to the transplant protocol. It's clear that KIR mismatching has an important role in the field of HSCT. Many algorithms have been made regarding the Graft versus leukemia(GvL) effects of NK cells and in near future we might even see the standard transplant protocol for Donor selection with KIR mismatching. Many transplant strategies using NK cells have also been published and research is still going on, its role in Haplo-identical Donor Selection, adoptive immunotherapy and malignant cells target. KIR is still the work in progress maybe in near future more role of KIR will be discovered not just in HSCT even for other diseases.

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