Impact of killer immunoglobulin-like receptor-human leukocyte antigens ligand incompatibility among renal transplantation

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ABSTRACT

Killer immunoglobulin-like receptor (KIR) gene shows a high degree of polymorphism. Natural killer cell receptor gets activated once they bind to self-human leukocyte antigens (HLAs) with specific ligand. KIR gene and HLA ligand incompatibility due to the presence/absence of KIR in the recipient and the corresponding HLA ligand in the allograft may impact graft survival in solid organ transplantation. This study evaluates the effect of matches between KIR genes and known HLA ligands. KIR genotypes were determined using sequence specific primer polymerase chain reaction. Presence of certain KIR in a recipient, where the donor lacked the corresponding HLA ligand was considered a mismatch. The allograft was considered matched when both KIR receptor and HLA alloantigen reveald compatibility among recipient and donor. The data revealed better survival among individuals with matched inhibitory KIR receptors and their corresponding HLA ligands (KIR2DL2/DL3-HLAC2, KIR3DL1-HLABw4). On the contrary, no adverse effect was seen for matched activating KIR receptors and their corresponding HLA ligands. One of the activating gene KIR2DS4 showed risk (P = 0.0413, odds ratio = 1.91, 95% confidence interval = 1.02-3.57) association with renal allograft rejection. We conclude that the presence of inhibitory KIR gene leads to better survival; whereas activating motifs show no significant role in renal allograft survival.

Key words: Acute renal allograft rejection, human leukocyte antigen-B, -C, killer immunoglobulin-like receptors, natural killer cells

Introduction

It has been shown that graft survival depends upon the compatibility of the human leukocyte antigens (HLAs). The immune mechanisms involved in graft survival are complex involving cellular and immunity T-cell activity is preceded by maturation of natural killer (NK) cell activity.[1]

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NK cells are reportedly increased in the acute rejection phase[2] and subsequently are observed to infiltrate renal allografts.[3] NK cells express inhibitory NK receptors, which can be activated by self HLA antigens (missing self-hypothesis) and get confronted with allogeneic cells lacking a ligand for a particular inhibitory receptor.

NK cell alloreactivity contributes to the immune response, which modulates the outcome of renal transplantation. NK cells have a central role in modulating the development of the adaptive response through interactions with HLA molecules on target cells. Under normal conditions, activation of NK cells is suppressed by dominant inhibitory signals.[4,5] Activation may therefore occur as a result of either a decrease in inhibitory signaling or an increase in the engagement of activating receptors.

HLAs act as ligands for NK cell expressed inhibitory and activating killer immunoglobulin-like receptors (KIRs), with subsequent modulation of NK cell function. KIRs are highly polymorphic and interact with the constitutively expressing HLA class-I ligands on the somatic cells.

The highly polymorphic KIR haplotypes are located on chromosome 19q13.4, that is broadly classified in Group A or B. The classification is based on the number and type of genes encoding inhibitory and activating KIRs. Group-A KIR haplotype comprises a fixed gene content of KIR3DL3-2DL3-2DL1-2DP1-3DP1-2DL4-3DL1-2DS4-3DL2. Haplotypes carrying any other combination of KIR loci are classified as Group-B haplotype.[6] There exist some particular KIR receptor-HLA ligand combinations namely: (1) HLA-C Group 1 (C1) specific for KIR 2DL2/3 with serine residue on 77th position and argenine at 80th position, (2) HLA-C Group 2 (C2) specific for KIR2DL1 has an argenine at 77th position and lysine at 80th position,[7] (3) HLA-Bw4 specific for KIR3DL1/DS1. Due to HLA and KIR polymorphism, in some combinations of the graft donor and recipient, recipient NK cell's inhibitory KIRs may not bind to HLA-I molecules present on donor cells, leading to NK cell alloreactivity against the transplanted organ.

In this study we evaluated the effect of KIR receptor-HLA ligand match/mismatch on the graft survival. The cases were stratified on the basis of presence/absence of KIR receptors among renal allograft recipients and their corresponding HLA ligands among donors.

Subjects and Methods

We investigated 277 renal allograft transplantation recipients (males = 235 [85%]) and their donors (males = 58 [21%]). Seventy-five patients suffered from either acute (n = 52) or chronic (n = 23) rejections.

For each patient, the information was collected for various factors such as age, gender, creatinine, urinary protein level, blood urea nitrogen, blood pressure, complete lipid profile, sodium, potassium, calcium, inorganic phosphate, alkaline phosphate. This work was approved by the Ethics Committees of the Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow. Informed consent was taken from all individuals and the study has been performed as per the Declaration of Helsinki. DNA was extracted from blood collected in ethylenediaminetetraacetic acid coated collection vials using Quiagen kits.

Killer immunoglobulin-like receptor and human leukocyte antigen genotyping

DNA samples were typed for the KIR genes responsible for inhibitory signals (2DL1, 2DL2, 2DL3, 3DL1, 3DL2, 3DL3, 2DL4, and 2DL5), those for activating signals (2DS1, 2DS2, 2DS3, 2DS4, 2DS5, and 3DS1), and two pseudo-genes 2DP1 and 3DP1, based on the primers described earlier.[8,9] Positive and negative controls were included in every reaction.[10] HLA-A, -B, -C typing was carried out using Invitrogen Gold sequence specific primer low resolution kits (Brown Deer, Wisconsin, USA).

Killer immunoglobulin-like receptor/human leukocyte antigen ligand incompatibilities associated with graft outcome

We calculated the number of matches for KIRs with known ligands (KIR2DL1/HLA-C2, KIR2DL2/HLA-C1, KIR2DL3/HLA-C1, and KIR3DL1/Bw4) and assumed HLA ligands (KIR2DS1/HLA-C2, KIR2DS2/HLA-C1, and KIR2DS3/HLA-C1). A condition was considered to be mismatched when the recipient displayed a certain KIR receptor but the donor graft did not have the corresponding HLA ligand. Similarly, the case where a defined KIR receptor was expressed by the recipient and the corresponding HLA ligand displayed by the allograft was considered to be matched.[11]

Survival analysis

Graft survival as analyzed using Kaplan-Meier survival analysis with log-rank test to compare the significance of difference between two groups. Death-censored graft survival was defined as death with a functioning graft (serum creatinine <6 ml/min/1.73 m^2) In the event of death with a nonfunctioning graft (serum creatinine >6 ml/min/1.73 m^2), the follow-up period was censored at the date of death. Death with graft function was treated as graft failure.[12]

Statistical analysis

Gene frequency of KIR was determined by direct counting. Frequencies of A and B haplotypes were calculated using the following formula: Group A = 2nAA + nAB/2N and Group B = 2nBB + nAB/2N, where nAA, nAB and nBB were the numbers of AA, AB and BB genotypes and N was the total number of individuals tested.[13] Frequency differences between the patient-donor pair as well as between rejection and nonrejection cases for inhibitory and activating KIR genes were tested for significance at 95% confidence limits using two-tailed Fisher's exact test with Bonferroni correction. To test whether a certain KIR gene profile is associated with acute rejection in a well characterized recipient/donor context, binary logistic regression was applied. $P \leq 0.05$ were considered significant. The magnitude of effect was estimated by odds ratio (OR) and their 95% confidence interval (CI). Graft survival rates were calculated according to the principle of Kaplan and Meier using SPSS (Statistical Package for the Social Sciences software version 16.0, IBM Corporation, New York, USA). Statistical significance was estimated using the log-rank test.

Results

Demographic and biochemical attributes

Samples were collected from those patients whose clinical details were available and were on a regular follow-up since last 12 years.

Killer immunoglobulin-like receptor gene frequency

Upon analyzing individual gene carriage frequency among 277 renal transplant patients with their donors, we observed significant protective association for KIR2DL1 gene (P = 0.0498, OR = 0.49, 95% CI = 0.25-0.95), whereas on comparing patients who underwent rejection (both chronic and acute) with those of nonrejection cases we got almost two-fold risk association with KIR2DS4 gene (P = 0.0413, OR = 1.91, 95% CI = 1.02-3.57) [Table 1].

Combinatorial effect of compatible killer immunoglobulin-like receptor/human leukocyte antigen ligand

Human leukocyte antigen-Bw4 acts as a ligand of KIR3DL1, while HLA-C1 is ligand for KIR2DL2/DS2 and KIR2DL3/DS3 and HLA-C2 binds with KIR2DL1/DS1. In this study, we have found significant protective association among KIR2DL2-HLA-C1/C1 (P = 0.0270, OR = 0.36, 95% CI = 0.14–0.89), KIR2DL3-HLA-C1/C1 (P = 0.0331, OR = 0.48,95%CI = 0.24-0.94) and KIR3DL1-HLA-Bw4/Bw6 (P = 0.0302, OR = 0.54, 95% CI = 0.31-0.94). On combining HLA-B homozygous and heterozygous groups protective association with KIR3DL1 (P = 0.0201, OR = 0.60, 95% CI = 0.40-0.92) was confirmed [Table 2].

Killer immunoglobulin-like receptor/human leukocyte antigen ligand incompatibilities associated with graft outcome

Upon applying binary logistic regression it was found that case where individual's allograft has a certain HLA allele, but its corresponding receptor remains absent in the recipient or cases where both HLA-allele and its matching receptor were absent showed a protective association. Such protective associations were observed for KIR2DL2-HLAC1 (P = 0.042, OR = 0.45, 95% CI = 0.20–0.97); KIR2DS1-HLAC2 (P = 0.048, OR = 0.42, 95% CI = 0.17-0.99); KIR3DS1-Bw4 (P = 0.004, OR = 0.26, 95% CI = 0.11-0.65). Similarly, protective association (P = 0.020, OR = 0.34, 95% CI = 0.11-0.65) was found when the patient have KIR3DS1 but the donor graft does not possess the corresponding HLA-Bw4 ligand [Table 3].

Survival analysis

The overall mean cumulative death censored graft failure of patients was 87 (95% CI = 84-91) months; while the mean cumulative graft survival of patients under the functioning graft failure category was 83 (95% CI = 77-89) months; and true graft failure category was 86 (95% CI = 84-89) months. The Mantel-Cox analysis gave a significant log-rank value, while comparing the survival duration among patients with true graft failure to that of patients with a functioning graft failure ($\chi 2$ = 4.81, P = 0.028). The overall mean cumulative patient survival was 8 (95% CI = 78-91) months [Figure 1]. Level of significance was obtained for KIR2DL1-HLAC2 9 ($\chi 2$ = 3.96, P = 0.047), KIR2DS1-HLAC2 ($\chi 2$ = 4.29, P = 0.038) and KIR3DL1-HLABw4 ($\chi 2$ = 4.05, P = 0.044) when the association of KIR-HLA ligand matches/mismatches on renal allograft rejection were estimated.

Killer immunoglobulin like-receptor 3DL1, KIR2DL1, and KIR2DL2 were observed to behave in a protective manner when investigated individually or in combination with different ligands. These results became more prominent upon survival analysis. The allograft recipients included in our study were followed-up-to 12 years. Kaplan-Meier survival analysis revealed that KIR3DL1-HLA-Bw4

Table 1: KIR gene frequency distribution among (i) ESRD versus healthy control and (ii) rejection versus nonrejection cases

KIR	*n*=277 (%)		*P* value	OR	95% CI	Rejection (*n*=75) (%)	Nonrejection (*n*=202) (%)	*P* value	OR	95% CI
	Patient	Donor								
KIR2DL1	234 (90)	247 (95)	0.0498*	0.49	0.25-0.95	68 (90)	185 (91)	0.8122	0.89	0.35-2.24
KIR2DL3	216 (83)	220 (84)	0.7209	0.89	0.55-1.42	60 (80)	165 (81)	0.7322	0.89	0.45-1.75
KIR2DL2	125 (45)	132 (51)	0.6093	0.90	0.64-1.26	37 (49)	111 (54)	0.4191	0.79	0.46-1.35
KIR2DL5	169 (61)	171 (61)	0.9305	0.97	0.68-1.36	51 (68)	141 (70)	0.7690	0.89	0.50-1.59
KIR3DL1	225 (81)	228 (87)	0.8259	0.92	0.60-1.43	67 (89)	182 (90)	0.8254	0.92	0.38-2.18
KIR3DL3	260 (100)	260 (100)	-	-	-	75 (100)	202 (100)	-	-	-
KIR2DL4	260 (100)	260 (100)	-	-	-	75 (100)	202 (100)	-	-	-
KIR3DL2	260 (100)	260 (100)	-	-	-	75 (100)	202 (100)	-	-	-
KIR2DS2	98 (37)	89 (34)	0.4653	1.16	0.81-1.66	28 (37)	72 (36)	0.8881	1.07	0.62-1.86
KIR2DS3	89 (34)	78 (30)	0.3481	1.21	0.83-1.75	25 (33)	64 (31)	0.8850	1.07	0.61-1.89
KIR3DS1	151 (58)	146 (56)	0.7237	1.08	0.76-1.52	41 (55)	107 (53)	0.8923	1.07	0.62-1.82
KIR2DS5	149 (54)	144 (52)	0.7335	1.07	0.77-1.50	39 (52)	101 (50)	0.7882	1.08	0.63-1.84
KIR2DS1	110 (40)	108 (41)	0.9307	1.03	0.73-1.45	31 (41)	82 (40)	1.0000	1.03	0.60-1.76
KIR2DS4	181 (70)	181 (70)	1.0756	1.00	0.68-1.45	59 (78)	133 (66)	0.0413*	1.91	1.02-3.57

*$P \leq 0.05$ and statistically significant. OR: Odds ratio, CI: Confidence interval, KIR: Killer immunoglobulin like receptor, ESRD: End stage renal disease

Table 2: KIR receptor-HLA ligand association among renal allograft rejection and nonrejection cases

HLA	KIR	Rejection (*n*=75) (%)	Nonrejection (*n*=202) (%)	*P* value	OR	95% CI
C1/C1	KIR2DL2+	6 (8)	39 (19)	0.0270*	0.36	0.14-0.89
	KIR2DL3+	13 (17)	61 (30)	0.0331*	0.48	0.24-0.94
	KIR2DS2+	9 (12)	23 (11)	0.8360	1.06	0.46-2.41
	KIR2DS3+	7 (9)	17 (8)	0.8122	1.12	0.44-2.82
C2/C2	KIR2DL1+	8 (11)	32 (16)	0.3385	0.63	0.27-1.44
	KIR2DS1+	7 (9)	17 (8)	0.8122	1.12	0.44-2.82
C1/C2	KIR2DL2+	18 (24)	51 (25)	0.8770	0.93	0.50-1.73
	KIR2DL3+	24 (32)	70 (35)	0.7755	0.88	0.50-1.56
	KIR2DS2+	15 (20)	32 (16)	0.4714	1.32	0.67-2.62
	KIR2DS3+	13 (17)	30 (15)	0.5820	1.20	0.58-2.45
	KIR2DL1+	29 (39)	81 (40)	0.8905	0.94	0.54-1.62
	KIR2DS1+	15 (20)	36 (18)	0.7277	1.15	0.58-2.25
Bw4/Bw4	KIR3DL1+	14 (19)	51 (25)	0.2691	0.67	0.35-1.31
	KIR3DS1+	12 (16)	21 (10)	0.2137	1.64	0.76-3.52
Bw6/Bw4	KIR3DL1+	25 (33)	97 (48)	0.0302*	0.54	0.31-0.94
	KIR3DS1+	19 (25)	-	1.0000	1.00	0.54-1.84
Combinatorial analysis						
Bw4/4+Bw4/6	KIR3DL1+	39 (52)	148 (73)	0.0201*	0.60	0.40-0.92
	KIR3DS1+	31 (41)	72 (36)	0.4619	1.20	0.75-1.92
Bw4/4+Bw6/6	KIR3DL1+	28 (37)	91 (45)	0.3534	0.78	0.49-1.26
	KIR3DS1+	22 (29)	41 (20)	0.1744	1.52	0.87-2.65

*$P \leq 0.05$ and statistically significant. No significance was obtained for HLA C1/C1+C1/C2, HLA C2/C2+C1/C2 and HLA C1/C1+C2/C2 combinations when compared with their respective KIR. KIR: Killer immunoglobulin like receptor, OR: Odds ratio, CI: Confidence interval, HLA: Human leukocyte antigens

Table 3: KIR-HLA ligand matches/mismatches among acute rejection and nonrejection cases using binary logistic regression

KIR-HLA ligand match-mismatch rejection (*n*=75)					KIR-HLA ligand match-mismatch nonrejection (*n*=202)					Mismatch			Missing		
KIR	HLA	Match (%)	Mismatch (%)	KIR/HLA± (%)	KIR	HLA	Match (%)	Mismatch (%)	KIR/HLA± (%)	*P* value	OR	95% CI	*P* value	OR	95% CI
KIR2DL2	HLA-C1	23 (30)	29 (38)	23 (30)	KIR2DL2	HLA-C1	61 (30)	78 (38)	63 (31)	0.154	0.59	0.28-1.21	0.042*	0.45	0.20-0.97
KIR2DL3	HLA-C1	40 (53)	15 (20)	20 (26)	KIR2DL3	HLA-C1	102 (50)	41 (20)	59 (29)	0.129	0.54	0.24-1.19	0.073	0.52	0.25-1.06
KIR2DS2	HLA-C1	18 (24)	40 (53)	17 (23)	KIR2DS2	HLA-C1	54 (27)	119 (59)	29 (14)	0.103	0.43	0.16-1.18	0.124	0.48	0.19-1.22
KIR2DS3	HLA-C1	12 (16)	46 (61)	17 (23)	KIR2DS3	HLA-C1	49 (24)	124 (61)	29 (14)	0.072	0.39	0.14-1.08	0.146	0.50	0.19-1.27
KIR2DL1	HLA-C2	34 (45)	24 (32)	17 (22)	KIR2DL1	HLA-C2	83 (41)	62 (30)	57 (28)	0.130	0.55	0.26-1.18	0.067	0.50	0.24-1.05
KIR2DS1	HLA-C2	15 (20)	29 (38)	31 (41)	KIR2DS1	HLA-C2	33 (16)	93 (46)	76 (37)	0.116	0.57	0.28-1.21	0.048*	0.42	0.17-0.99
KIR3DL1	HLA-Bw4	35 (46)	21 (28)	19 (25)	KIR3DL1	HLA-Bw4	107 (53)	33 (16)	62 (30)	0.608	1.20	0.58-2.49	0.166	0.63	0.32-1.21
KIR3DS1	HLA-Bw4	27 (36)	31 (41)	17 (23)	KIR3DS1	HLA-Bw4	65 (32)	91 (45)	46 (23)	0.020*	0.34	0.14-0.84	0.004*	0.26	0.11-0.65

*$P \leq 0.05$ and statistically significant. Match: KIR receptor is expressed by the recipient and the corresponding HLA ligand is displayed by the allograft, Mismatch: Recipient displays a certain KIR receptor but the donor graft does not have the corresponding HLA ligand, KIR/HLA± (missing): When the allograft has a certain HLA allele but the recipient is lacking the corresponding receptor; or when recipient and allograft both are lacking the receptor as well as the corresponding HLA ligand, KIR: Killer immunoglobulin like receptor, OR: Odds ratio, CI: Confidence interval, HLA: Human leukocyte antigens

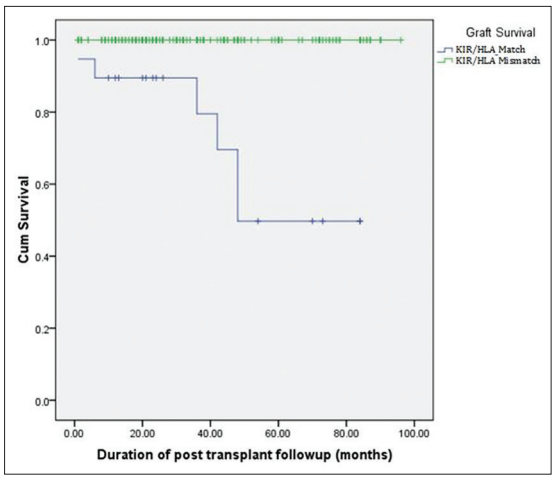

Figure 1: Survival plot among killer immunoglobulin-like receptor and human leukocyte antigen-ligand match/mismatch cases

provides the highest overall survival of approximately 11 years when compared to KIR2DL1-HLA C2 (7 years survival) and KIR2DL2-HLA C1 (5 years survival).

Discussion

In solid organ transplantation, NK cells show the ability to distinguish allogeneic MHC antigens in conjunction with KIR receptors. NK cells recognize HLA present on all cells through activator and inhibitor cell surface receptors, including KIRs. All KIRs are randomly expressed on NK cells, which are educated to self-HLA. This event occurs when the mature KIRs vary genetically among individuals and the balance of KIR activating and inhibiting signals regulate NK cell function. Donor NK cells mediate an anti-allograft effect in recipients

when inhibitory KIRs are mismatched for HLA type I transplants since these cells recognize recipient allograft cells as foreign.[14] The mismatched donor NK cells can decrease the rate of relapse. However, the mismatched transplant also has an increased risk of graft versus host disease (GvHD). NK cell function is regulated by KIR interactions with matched HLA class I alleles. For inhibitor KIRs, binding with matching HLA prevents donor NK cell activation to self. For activating KIRs, donor NK cells that bind the matched HLA are activated and induce cell lysis in the recipient transplant [Figure 2]. The same approach has been applied to test whether HLA epitope disparity influences NK alloreactivity of the donor in the renal transplant setting.[15]

In this study, we have observed the prevalence of HLA-Bw4/KIR3DL1 matched cases among ESRD (~53%) showing ~ 11 years of survival followed by HLA-C2/KIR2DL2 matched cases (~41%) showing survival of ~7 years. While the activating KIR receptor associated HLA-Bw4/KIR3DS1 and HLA-C1/KIR2DS1 combinations showed a reduced survival rate among the renal graft rejection cases. The combinatorial analysis revealed protective association for HLA-Bw4/KIR3DL1. The renal graft rejection cases were classified on the basis of serum creatinine level into true rejection (serum creatinine >6 ml/min/1.73 m^2) and rejection with a functioning graft (serum creatinine <6 ml/min/1.73 m^2). Subsequently, the cases were compared on the basis of KIR-HLA match-mismatch criteria. We found prolonged survival for rejection with functioning graft cases in comparison to cases under true rejection category. Further combinatorial analysis revealed significant protective associations of KIR2DL2-HLAC1, KIR2DL3-HLAC1, and KIR3DL1-HLABw4 combinations for ESRD patients.

Earlier reports suggested that donor cells having one homozygous HLA-Cw polymorphism would be at risk for lysis by recipient NK cells if the recipient is either heterozygous or homozygous. For the other HLA-Cw polymorphism patients mismatched for HLA-Cw may not have the correct repertoire of KIR to enable them to be activated by donor cells. Moreover, recipients heterozygous for HLA-Cw would recognize donor cells from either group as self and therefore should not be considered allospecific. Certain combinations of KIR-HLA haplotypes have also been linked with susceptibility to the risk of preeclampsia,[10] HIV infection,[16] or autoimmune diseases,[17,18] but susceptibility could be due to reduced NK cell inhibition, when an individual is homozygous for HLA-C1 alleles and lacks a ligand for KIR2DL1 and those homozygous for HLA-C2 lack the corresponding ligand for KIR2DL2/3.

In one of our earlier report,[19] we have found risk associations for activating KIR genes 3DS1, 2DS2, 2DS3, 3DS1, 2DS5, and 2DS1 for ESRD cases. However, in this study taking into consideration the acute allograft

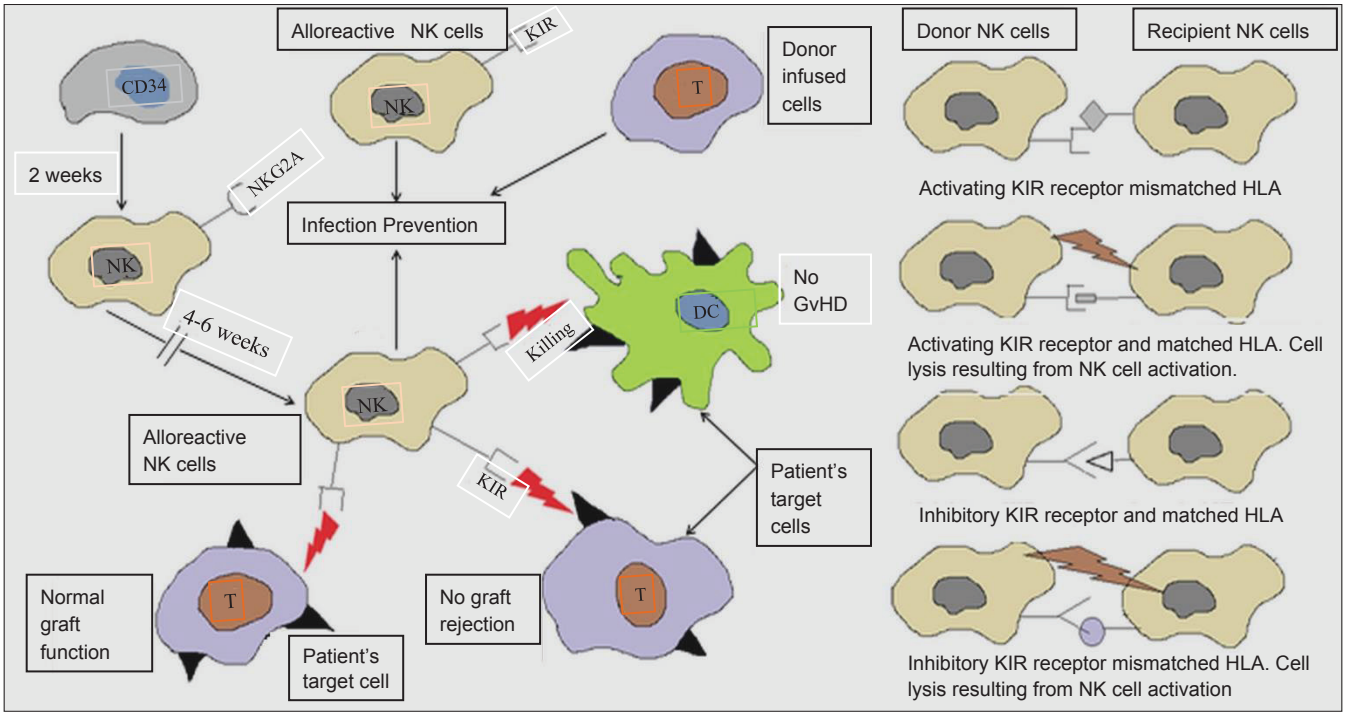

Figure 2: Effect of natural killer (NK) cell regulation on graft rejection and graft versus host disease. NK cell function is regulated by killer immunoglobulin like receptor (KIR) interactions with matched human leukocyte (HLA) class I alleles. In the case for inhibitor KIR, binding with matching HLA prevents donor NK cell activation to self

rejection cases, level of significance was attained only for KIR2DS4. Earlier reports have shown similar risk association for KIR2DS4 with acute renal allograft rejection.[20,21] Interestingly, it has also been suggested that the presence of KIR2DS4 gene affected kidney graft rejection stronger than HLA incompatibility.

Killer immunoglobulin like-receptors are allotype and isotype specific. Thus, allografts with mismatched HLA molecules can potentially be recognized and killed. KIR and HLA are present on different chromosomes and therefore are differently inherited. However, much less is known about the comparative expression of inhibitory and activating KIRs on T-cell subsets during posttransplant period among renal transplantation cases. During allograft rejection two categories of alloreactive NK cells come into play that is the cells separated from CD34+ cells after 6-8 weeks from transplantation and the freshly infused donor cells into allograft recipients. Availability of alloreactive effector cells may improve the survival of allograft by removal of residual allograft recipient's dendritic cells and T-lymphocytes. This ensures efficient prevention of graft rejection and GvHD. Further the transplanted NK cells will provide first line of defense against different infectious agents [Figure 2]. Impact of NK cells in transplant rejection remained debatable as increased overall survival, reduced incidence of GvHD and better engraftment has been linked to KIR-HLA ligand mismatch with haploidentical allogeneic stem cell transplantation in acute myeloid leukemia cases.[22] This is attributed to the NK cell mediated clearance of residual leukemia cells (decreased relapse rate), host T cells (better engraftment) and host dendritic cells (reduced GvHD). Thus, it may be predicted that NK cells are not unfavorable to the survival of the graft. However in the context of allogeneic stem cell transplantation across MHC-compatible pairs can generate NK cell cytotoxicity due to KIR-HLA match/mismatch.[23] Similarly, the same approach resulted in decreased survival following KIR-HLA ligand mismatched allografts in some other studies.[24] These results have been attributed to the heterogeneity of treatment protocols and patient cohorts.

These study findings suggest that a particular set of activating KIR receptor-HLA ligand repertoires might predispose to acute allograft rejection, while another set of inhibitory KIR receptor-HLA ligand repertoires might play a role in prolonged allograft survival. Studies are required to address the receptor ligand interaction in the context of solid organ transplantation vividly in order to understand how HLA-KIR genotypes contribute to transplant outcome, which may ease the graft survival and prognosis of renal allograft rejection.

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