

# Importance of Non-HLA Gene Polymorphisms in Hematopoietic Stem Cell Transplantation

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## 1. Introduction

In the last 10 years, non-HLA genotypes have been investigated for their potential roles in the occurrence and severity of graft-versus-host disease (GvHD) as well as for their contribution to overall transplant-related mortality, infectious episodes, and overall survival.

These non-HLA-encoded genes include polymorphisms within the regulatory sequences of the cytokine genes, or genes associating with innate immunity: *KIR* (killer immunoglobulin-like receptor) genes, *MIC* (MHC class I chain-related) genes, and others.

The first studied non-HLA genes were polymorphisms in regulatory cytokine genes because of cytokine role in GvHD immunopathogenesis. Single nucleotide polymorphisms in several regions of cytokine genes were correlated with the transplant overcome in several studies (Kim et al., 2005; Laguila Visentainer et al., 2005; Lin et al., 2003; Mlynarczewska et al., 2004; Viel et al., 2007; reviewed in Dickinson, 2008).

## 2. Role of cytokines in graft-versus-host disease after allogeneic stem cell transplantation

The pathophysiology of acute GvHD can be considered a cytokine storm (Ferrara, 2000), initializing with the transplant conditioning regimen that damages and activates host tissues. Activated host cells secrete inflammatory cytokines, such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1. This initial cytokine release is further amplified in the second phase by presentation of host antigens to donor T cells and the subsequent proliferation and differentiation of these activated T cells. These cells secrete a variety of cytokines, such as IL-2, TNF- $\alpha$ , interferon (IFN)- $\gamma$ , IL-4, IL-6, IL-10, and transforming growth factor-beta (TGF)- $\beta$ 1. Several reports have demonstrated the increase of these cytokines in the serum from patients with acute GvHD (Kayaba et al., 2000; Liem et al., 1998; Sakata et al., 2001; Visentainer et al., 2003).

Although chronic GvHD remains a frequent complication of hematopoietic stem cell transplantation (HSCT), the pathogenesis is still unclear. However, it is known that cytokines also play an important role in its development (Iwasaki, 2004; Letterio & Roberts, 1998; Liem et al., 1999; Margolis & Vogelsang, 2000; Zhang et al., 2006). Chronic GvHD is a multisystem alloimmune and autoimmune disorder characterized by immune

dysregulation, immunodeficiency, impaired organ function and decreased survival (Baird & Pavletic, 2006). It starts with the expansion of donor T cells in response to allo or auto-antigens that escape assessment thymus and the mechanisms of deletion. T cells induce damage in target organs by attacking cytolytic, inflammatory cytokines and fibrosis by activating B cells, with production of autoantibodies (Pérez-Simón et al., 2006).

Thus multiple cytokines are important in GvHD pathogenesis and regulation (Ferrara & Krenger, 1998; Jung et al., 2006; Kappel et al., 2009; Reddy et al., 2003; Tawara et al., 2008; Visentainer et al., 2005; Yi et al., 2008). Furthermore, the timing and duration of cytokine expression may be a critical factor determining the induction of the graft-versus-host (GvH) reaction, and cytokine dysregulation could potentially contribute to the severity of GvHD.

Recently, Choi et al. (2010) and Paczesny et al. (2010) reviewed the biology of acute GvHD, and concluded that the underlying mechanisms of GvHD have emerged as a complex network of immune interactions where the key players are the naive T cells, the host and donor APCs, CTLs and regulatory T cells, along with new players such as Plasmacytoid DCs (pDCs), B cells and Th17 cells.

### **2.1 Cytokine gene polymorphisms**

The production of some cytokines is under genetic control. Polymorphisms in the regulatory regions of several cytokine genes may cause inter-individual differences in cytokine production (Wilson et al., 1997; Turner et al., 1997; Awad et al., 1998; Fishman et al., 1998; Pravica et al., 1999). As these polymorphisms segregate independently, each person is a mosaic of high-, intermediate-, and low-producing phenotypes. These cytokine polymorphisms are known to have functional relevance in post-transplant outcome, rejection and GvHD, following solid organ (Benza et al., 2009; Fernandes et al., 2002; Hahn et al., 2001; Karimi et al., 2011; Reviron et al., 2001) and hematopoietic stem cell transplantation (Ambrozova et al., 2009; Karimi et al., 2010; Laguila Visentainer et al., 2005; Leffell et al., 2001; Takahashi et al., 2000; Tambur et al., 2001), respectively.

### **2.2 Impact of cytokine gene polymorphisms on graft-vs-host disease**

Many studies in recent years have focused on correlating donor and/or recipient genotype with GvHD risk. Table 1 summarizes the various polymorphisms in genes encoding both pro- and anti-inflammatory factors and their receptors that have been studied in GvHD.

## **3. Killer immunoglobulin-like receptors and hematopoietic stem cell transplantation**

Natural killer (NK) cell effector function is regulated by a balance between activating receptors and inhibitory receptors for major histocompatibility complex (MHC) class I molecules (Joyce & Sun, 2011; Parham et al., 2006; Yokoyama et al., 2006). In the setting of allogeneic HSCT, donor NK cells may attack recipient cells that lack the appropriate HLA class I ligands for the donor KIR. Several studies have shown that certain combinations of killer immunoglobulin-like receptors and human leukocyte antigens (in both donors and recipients) can affect the chances of survival of transplant patients, particularly in relation to the graft-versus-leukemia effect, which may be associated to decreased relapse rates in certain groups (reviewed in Franceschi et al., 2011).

GvHD		
Acute	Chronic	
SNP/Genotype		References
	<i>IL1A</i> -889*2	Cullup et al. (2003)
<i>IL6</i> -174 G/C	<i>IL6</i> -174 GG	Lin et al. (2003)
	<i>IL6</i> -174 CC	Laguila Visentainer et al. (2005)
<i>TNF</i> -308 GG/GA		Takahashi et al. (2000)
	<i>TNF</i> -238 GA	Viel et al. (2007)
<i>IL2</i> -330 GT		Macmillan et al. (2003)
	<i>IL10</i> -1082,-819,-592 ATA/ATA	Kim et al. (2005)
<i>IL10</i> -592 A/A		Lin et al. (2003)
<i>IL</i> -10RB A/A	<i>IL</i> -10RB A/A	Sivula et al. (2009)
<i>TGFB1</i> +869,+915 TG/GG		Leffell et al. (2001)
<i>TGFB1</i> +869 T		Hattori et al. (2002)
<i>TGF</i> - <i>beta</i> 1 codon 25 GG		Rashidi-Nezhad et al. (2010)
<i>IFN</i> - $\gamma$ T+874A		Karimi et al. (2010)
<i>IL</i> -7RA		Shamim et al. (2011)

Table 1. Polymorphisms in genes encoding both pro- and anti-inflammatory factors and their receptors in GvHD

### 3.1 Killer immunoglobulin-like receptors

The group of *KIR* genes comprises a region of approximately 150 Kb in the leukocyte receptor complex (LRC) on chromosome 19q13.4 (Uhrberg et al., 1997). KIRs are members of a group of regulatory molecules on the surface of NK cells, in subgroups of  $T\gamma\delta$ + lymphocytes, effector  $T\alpha\beta$ + lymphocytes and memory lymphocytes (Rajagopalan & Long, 2005). The KIR family includes activating and inhibitory molecules. Inhibitory KIRs (2DL and 3DL) have a long cytoplasmic tail containing tyrosine-based inhibitory motifs (ITIMs) that trigger inhibitory events of cytotoxicity. In contrast, activating KIRs (2DS and 3DS) interact with the DAP12 molecule, which has tyrosine-based activation motifs (ITAMs) that cause a cascade that results in an increase in cytoplasmic granulation and the production of cytokines and chemokines, thereby initiating immune response (McVicar et al., 2001).

The balance between activation and inhibition of NK cells occurs through the binding of KIRs with HLA class I molecules present in all nucleated cells of an individual. Most KIRs bind to HLA-C molecules. It is worth remembering the importance of the dimorphism of amino acids, such as residue 80 of  $\alpha$ -helix-1, in the definition of this HLA receptor. On this basis, HLA-C alleles may be defined as "Group 1" or "Group 2": C1 - HLA-Cw\*01, \*03, \*07, \*08, \*12, \*13, \*14, and \*16 and C2 - HLA-Cw\*02, \*04, \*05, \*06, \*07, \*15, \*17, and \*18, which are specific for KIR2DL2/2DL3/2DS2 and KIR2DL1/2DS1, respectively (Boyton & Altmann, 2007). Evidence suggests that HLA-Cw4 is a receptor for KIR2DS4 (Katz et al., 2001). The KIR2DL4, for example, specificity binds to the HLA-G molecule (Rajagopalan & Long, 1999), while the KIR3DL1 receptor binds to a subset of HLA molecules with the Bw4 epitope, present in approximately one third of all HLA-B molecules. The KIR3DS1 is highly homologous with 3DL1 and seems to share the Bw4 epitope as ligand, although this needs to be experimentally verified. The KIR3DL2 receptor is still being discussed, but studies suggest that HLA-A3 and HLA-A11 perform this role (O'Connor et al., 2006).

Based on the genetic content and pattern of segregation at the population level, *KIR* haplotypes are divided into two groups, A and B, varying in the type and number of genes present. The *KIR* group A haplotype is uniform in terms of gene content (*3DL3*, *2DL3*, *2DL1*, *2DP1*, *3DP1*, *2DL4*, *3DL1*, *2DS4*, and *3DL2*), of which all but 1 encode inhibitory receptors. In contrast, the *KIR* group B haplotype is more diverse in the *KIR* genes it contains, has more activating receptors, and is characterized by the *2DL2*, *2DS1*, *2DS2*, *2DS3*, and *2DS5* genes (Uhrberg et al., 1997).

### 3.2 Impact of killer immunoglobulin-like receptors and hematopoietic stem cell transplantation

Previous studies have examined the effect of donor and recipient *KIR* genotypes on the outcome of allogeneic HSCT (Bishara et al., 2004; Gagne et al., 2002; Sun et al., 2005). One study found a 100% risk of GvHD after unrelated donor BMT, when the donor contained *KIR* genes absent in the recipient, compared to a 60% risk of GvHD with other combinations (Gagne et al., 2002).

In 2004, one study carried out *KIR-HLA* genotyping of 220 related HLA identical donor-recipient pairs (112 for myeloid diseases and 108 lymphoid diseases) (Cook et al., 2004). For patients with myeloid diseases, survival was lower in those homozygous for Group 2 (C2) HLA-C compared to patients with Group 1 (C1). This effect was observed only when the donor had the *KIR2DS2* gene. As *KIR2DS2* is in strong linkage disequilibrium with *KIR2DL2* (receptor inhibited by C1), this would indirectly indicate lower survival in patients who do not have the receptor for *KIR2DL2*, an opposite result to the model in which this lack of inhibition could result in NK cell alloreactivity with a consequent elimination of residual leukemic cells (Witt et al., 2006). In 178 patients with AML, CML, ALL and primary myelodysplastic syndrome (MDS) who received HSCT with T cell depletion from HLA-identical related donors, some authors observed that the disease-free survival was significantly higher in patients with AML and MDS that did not have the HLA ligand for the inhibitory *KIR* of the donor (Hsu et al., 2005). Moreover, the relapse rate was lower in these individuals, which may be related to higher survival rates. The results differ from a study in which T cell depletion was not performed (Cook et al., 2004). In another study (Schellekens et al., 2008) involving 83 patients with different types of hematologic malignancies who received HSCT from related HLA-identical donors without T cell depletion, a high relapse rate was found when high numbers of activating *KIRs* were present in both the patient and donor. According to the authors, a consequence of this finding may be an increased alloreactivity of the host against graft, impairing the response of donor cells resulting in an insufficient graft-versus-leukemia effect and increased risk of leukemic relapse.

Nowadays, there is no unequivocal evidence that polymorphic genes for *KIR* involved in innate immunity sufficiently influence GvHD and transplant outcome to change clinical practice (Davies et al., 2002; Cooley et al., 2009; Giebel et al., 2003; Hsu et al., 2005; Ludajic et al., 2009; Miller et al., 2007; Moretta et al., 2009; Schellekens et al., 2008; Symons et al., 2010; Witt et al., 2006).

Using a large cohort of patients, Venstrom et al. (2010) demonstrated that individual donor activating *KIR*, recipient HLA class I ligands, and donor *KIR* gene copy number all impact *KIR*-driven NK effects. They also showed that not all *KIR* B haplotypes have equivalent clinical impact, and they proposed that future studies consider specific B haplotype subsets or individual *KIR* genes in their analyses.

However, there are conflicting results in many studies, which may be due to the heterogeneity in HSCT protocols employed, differences in inclusion criteria, the HSCT preparative regimen and graft content, the degree of donor HLA-incompatibility, and posttransplant immunosuppression. Beside of this, according to early studies, Symons et al. (2010) have described 4 models of NK cell alloreactivity to predict HSCT outcomes: 1) KIR ligand incompatibility; 2) receptor-ligand model; 3) missing ligand model; and 4) *KIR* gene-gene model. And, contradictory results obtained from these models have made it difficult to conclude which model is most predictive of transplant outcome.

#### **4. *MICA* and *MICB* matching in bone marrow transplantation**

Retrospective and prospective studies have shown that matching donors and recipients for non-HLA DNA sequences in the MHC (beta and delta block matching) can result in improved patient survival and less severe GvHD (Tay et al., 1995; Witt et al., 2000). One of these blocks, the beta block, spans about 300 kb and contains the immunologically relevant *HLA-B*, *HLA-C*, *MICA*, and *MICB* genes (Kitcharoen et al., 2006). The polymorphic *MICA* molecule likely may be a target for specific antibodies and T cells in solid organ grafts or in GvHD (Zhang & Stastny, 2006).

##### **4.1 *MICA* and *MICB* genes**

In 1994, two new polymorphic families of MHC class I related genes, termed MHC class I-related chain A (*MICA*) and B (*MICB*) were described (Bahram et al., 1994). These genes are highly polymorphic with at least 76 alleles for *MICA* and 31 alleles for *MICB* (IMGT/HLA database; <http://www.ebi.ac.uk/imgt/hla/stats.html>), and are located in the MHC classical class I region (Horton et al., 2004), 46.4 and 141.2 kb centromeric to *HLA-B*, respectively (Bahram et al., 1994; Bahram et al., 2000; Leelayuwat et al., 1994). They encode cell surface glycoproteins that do not associate with  $\beta_2$ -microglobulin. These molecules function as restriction elements for intestinal  $\gamma\delta$  T cells and they behave as cell stress molecules. *MICA* is expressed in endothelial cells, keratinocytes and monocytes, but not in CD4+, CD8+ or CD19+ lymphocytes (Zwirner et al., 1999).

The *MICA* gene products have been shown to play a role in some aspects of antigen presentation and T-cell recognition, and appear to be important in innate immunity as ligands to NKG2D receptor expressed on most  $\gamma\delta$  T cells, CD8  $\alpha\beta$  T cells, and NK cells (Tieng et al., 2002).

##### **4.2 *MICA* and *MICB* and relevance to stem cell transplantation outcome**

Several studies have shown that the highly polymorphic MIC antigens are expressed in transplanted organs and may cause early graft rejection (Hankey et al., 2002; Mizutani et al., 2006; Narayan et al., 2011; Panigrahi et al., 2007; Sumitran-Holgersson, 2008; Terasaki et al., 2007). The polymorphisms of *MICA* and *MICB* may be involved in allogeneic BMT and GvHD (Gannage et al., 2008; Murai et al., 2003; Parmar et al. 2009; Przepiorka et al., 1995) because they are augmented by stress in epithelia (Groh et al., 1996) and are recognized by a subpopulation of intestinal  $\gamma\delta$  T cells (Zou et al. 2007). In addition to classical HLA class I and II matching, matches at *MICA* and *MICB* loci have been shown to increase patient survival (Kitcharoen et al., 2006).

Recent review has discussed the genetics and biology of the *MICA* gene and its products, and their importance in disease related to NK activity and allograft rejection or GvHD

(Choy & Phipps, 2010). According to Parmar et al. (2009), some HSCT cases with matched HLA but mismatched MICA showed an increased incidence of GvHD, and according to Boukouaci et al. (2009), MICA-129 valine and soluble MICA are risk factors for chronic GvHD, whereas the presence of anti-MICA antibodies that can neutralize soluble MICA confers protection.

A methionine to valine change at position 129 of the  $\alpha$ 2-heavy chain domain categorized the MICA alleles into strong (MICA-129 met) and weak (MICA-129 val) binders of NKG2D receptor (Steinle et al., 2001). Varying affinities of MICA alleles for NKG2D may affect thresholds of NK-cell triggering and T-cell modulation. According to Boukouaci et al. (2009), in the context of cGVHD, the weak engagement of NKG2D receptors by the weak binder MICA-129 val allele may impair NK/cytotoxic T lymphocyte cell activation/costimulation, possibly skewing the TH1 pathway toward TH2 with consequent B-cell activation and Ab production.

## 5. Conclusion

Analysis of non-HLA genetics may permit more accurate assessment of transplant-related complications, improve donor selection and individualized prophylaxis, and aid in the development of a prognostic risk index. Overall, this type of analysis could potentially define high- and low-risk patient groups, and to result in effective therapeutic strategies for GvHD.

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