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Genetics of Graft-versus-Host Disease: The Major Histocompatibility Complex

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Abstract

Graft-versus-host disease (GVHD) is a potentially life-threatening complication of allogeneic hematopoietic cell transplantation. Many genes are presumed to be involved in GVHD, but the best characterized genetic system is that of the human major histocompatibility complex (MHC) located on chromosome 6. Among the hundreds of genes located within the MHC region, the best known and characterized are the classical HLA genes, HLA-A, C, B, DRB1, DQB1, and DPB1. They play a fundamental role in T cell immune responses, and HLA-A, C, and B also function as ligands for the natural killer cell immunoglobulin-like receptors involved in innate immunity. This review highlights the state-of-the art in the field of histocompatibility and immunogenetics of the MHC with respect to genetic risk factors for GVHD.

Keywords

Major histocompatibility complex (MHC); HLA; Haplotype; Linkage disequilibrium (LD); Graft-versus-host disease (GVHD); Hematopoietic cell transplantation (HCT); Unrelated donor; Cord blood transplantation; Single nucleotide polymorphism (SNP)

Introduction

The major histocompatibility complex (MHC) is a 7 megabase gene-rich region on chromosome 6p21. A staggering number of genes within the MHC participate in immune responses. This review will focus on the role of classical HLA, non-classical HLA, and haplotype-linked inflammatory genes in GVHD after hematopoietic cell transplantation (HCT) from unrelated and haploidentical related donors and cord blood graft sources. New research on mapping novel MHC region genes involved in GVHD is presented.

I. Classical HLA Genes

In 1954, Professor Jean Dausset described a white blood cell antigen named “HU-1” [1]. Shortly thereafter, Professors Jon van Rood and Rose Payne defined a series of novel iso-antigens, which earned the name “LA” [2;3]. Therein marked the beginning of the HLA (**H**U-1 and **LA**) system as we know it today [4;5]. As of September, 2012, there are over 2,013 HLA-

Conflict of Interest: None.

A, 1,551 HLA-C, 2,605 HLA-B, 1,159 HLA-DRB1, 126 HLA-DQB1 and 155 HLA-DPB1 alleles recognized by the World Health Organization Nomenclature Committee for Factors of the HLA System [6]. Since its discovery over 50 years ago, there has been extensive scientific investigation into the functional implications of HLA genetic diversity. The availability of molecular tools for typing allelic variants of HLA genes has in large part contributed to the log rhythmic increase in information on the role of HLA genes in transplantation.

A. Association of Genotypes with GVHD—The MHC has the most extensive number of associations to human diseases than any other region of the human genome [7]. Whether specific HLA genotypes also serve as prognostic indicators of GVHD has been an area of active investigation [8-12]. These studies test the hypothesis that GVHD is influenced by peptides presented as minor histocompatibility antigens by specific HLA antigens. In a large single center analysis, individual HLA types were evaluated in over 2,500 patients transplanted from HLA-identical sibling donors [12]. There was evidence for global heterogeneity in risk of GVHD associated with HLA-B tissue type, and a trend for lower risk of GVHD in HLA-B35-positive and B49-positive patients. Since the associations between HLA-B phenotype and GVHD risk in this study were consistent with some [8] but not other analyses [9], the authors concluded that there was a lack of biologically plausible associations of HLA-B antigens with GVHD risk. Since tissue types were defined at the serological level, the potential still exists that unique DNA-defined alleles may be GVHD risk markers.

1. HLA-DR15 Haplotypes: HLA-DR15 has been a haplotype of great interest because of its association with several immune-mediated marrow failure syndromes including severe aplastic anemia, myelodysplastic syndrome (MDS), and paroxysmal nocturnal hemoglobinuria [13-21]. Furthermore, the presence of HLA-DR15 influences the response to immunosuppressive therapy in these disorders [16;22-25].

The association of HLA-DR15 to acute and chronic GVHD, relapse and survival has been explored in several transplant populations [21;26-29]. In an early analysis of 167 patients receiving a related or unrelated HLA-matched transplant for myeloid diseases, the presence of HLA-DR15 was associated with a lower risk of grades II-IV acute GVHD (23% versus 42%, P = 0.04) but not with chronic GVHD [26]. In contrast, an independent study of 192 HLA-identical sibling transplants for acute or chronic leukemia or non-Hodgkin lymphoma identified HLA-DR15 as a beneficial marker of transplant outcome [27]. Patients carrying HLA-DR15 had higher five-year survival (76% versus 55%, P = 0.04) that was likely due to lower relapse (5% versus 24%, P = 0.02) when compared to HLA-DR15-negative patients. Similar beneficial trends were reported in a series of 286 patients who received HLA-identical sibling transplants [28]. Most recently, an analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) included 1,204 patients receiving transplants from HLA-identical siblings for severe aplastic anemia [29]. Secondary graft failure was lower in HLA-DR15-positive patients (HR .46, P = 0.01), however neutrophil recovery, platelet recovery, acute and chronic GVHD and survival were not associated with presence of HLA-DR15.

How can these differences be reconciled? The answer may in part be found in haplotype-linked variation within the tumor necrosis factor (TNF) gene located in the class III region of the MHC [21]. In a retrospective study of 7,950 patients transplanted for benign and malignant blood diseases, risks after transplantation were not the same for patients with MDS or chronic myeloid leukemia (CML) and depended on HLA-DR15 haplotype-linked variation within the TNF genetic region [21]. In this study, patients with MDS were more often HLA-DR15-postive (31%) than patients with CML (23%). Among MDS and CML

patients, HLA-DR15 was not associated with GVHD, relapse, non-relapse mortality (NRM) or survival. Haplotype-linked TNF polymorphisms, however, differed at the -308 position in the TNF promoter where the AG genotype was associated with increased NRM compared to the GG genotype (HR 1.49, P = 0.02) after adjusting for the presence of HLA-DR15. Furthermore, at the -863 position, the AA genotype was associated with lower mortality (HR 0.36, P = 0.04) and NRM (HR 0.13, P = 0.04) compared to the CC genotype after adjusting for HLA-DR15. Interestingly, the impact of TNF polymorphisms on grades II-IV acute GVHD depended on whether the genotypes were carried on HLA-DR15 haplotypes. In HLA-DR15-negative patients, -308AG was associated with an increased risk of acute GVHD compared to patients with GG genotypes; however, -308AG in HLA-DR15-positive patients was protective. Neither position was associated with transplant outcome in patients with CML. Therefore, the risks associated with HLA-DR15 positivity among patients with MDS were influenced by the haplotype-liked TNF variation and not by HLA-DR15 *per se*. No association with HLA-B alleles and transplant outcome was observed. These results suggest that haplotypes, by virtue of their gene content and sequence diversity, may confer different risks of GVHD. Efforts to map haplotype-specific variation are likely to yield promising new information that can be used to assess risks of GVHD in patients prior to transplantation. A review of current studies aimed at mapping MHC haplotype-linked variation is presented below.

2. Non-classical Class I Genes and GVHD: HLA-E, HLA-G, and MICA: The class I region encodes the classical loci HLA-A, C, and B, as well as the non-classical genes HLA-E, HLA-G and MICA. HLA-E has been of particular interest because HLA-E molecules are ligands for the inhibitory natural killer (NK) cell receptor NKG2A [30] and may also be involved in allele-specific presentation of minor histocompatibility antigens [31]. Since a model that proposes genotype-associated risk does not depend on patient-donor HLA mismatching, the presence of specific HLA-E alleles could affect the risk of GVHD after HLA-matched or mismatched related or unrelated donor HCT much in the same way as the classical HLA antigens described above. Several studies have identified an association of specific HLA-E alleles with transplant outcome, although these studies arrive at different conclusions regarding the endpoints most affected. Whereas a protective effect of the E*01:03 allele on GVHD was observed in sibling and unrelated donor HCT [32;33], the same allele led to lower transplant-related mortality (TRM) and better survival (but not acute GVHD) in other studies [34;35]. Yet, new information from an independent study of unrelated donor transplants does not suggest any correlation between HLA-E alleles and transplant outcome [36]. Hence, a role for specific HLA-E alleles in GVHD remains to be defined.

Whereas HLA-E is ligand for inhibitory NK receptors, MICA is a ligand for the activating NKG2D receptor. Patients who are homozygous for a valine at residue 129 of MICA are at higher risk for chronic GVHD after HLA-matched sibling HCT compared to patients who have a methionine at this position; risk was independent of acute GVHD, suggesting a role for residue 129 in alloimmune responses [37]. The role of patient-donor mismatching at MICA is described below.

HLA-G has been most intensely studied as a key molecule in maternal-fetal immunology. Studies in HCT have focused on a 14 basepair (bp) sequence within the gene that correlates with the level of HLA-G expression. The 14-bp deletion is associated with high levels of HLA-G expression whereas the 14-bp insertion is associated with lower levels. Studies that have investigated the relationship between GVHD and the 14 bp sequence have yielded heterogeneous results. The 14 bp deletion was associated with an increased risk of acute GVHD after unrelated donor HCT [38] and with lower survival and disease-free survival (DFS) [39], however in another analysis, the 14 bp insertion most closely predicted risk of clinically severe acute GVHD [40]. These results likely reflect population differences and

complex mechanisms that involve splice variants of HLA-G [41-43]. Future studies of HLA-G are needed to bridge the molecular with phenotypic variation defined by the insertion/deletion polymorphism on GVHD risk.

B. Impact of Mismatching for Classical HLA Genes on GVHD—Donor HLA mismatching is one of the best characterized risk factors for GVHD in transplantation from related and unrelated donors and cord blood units. The principles of HLA matching have been most extensively elucidated in unrelated donor transplantation, which has served as a starting point for investigation in cord blood transplantation. The following section summarizes the rich history of studies investigating the importance of HLA matching in HCT.

1. Unrelated Donor Transplantation: There are 5 major concepts regarding the role of donor HLA mismatching and GVHD in unrelated donor HCT: 1) type and match at high resolution; 2) consider HLA-DP especially if HLA-A, C, B, DR, DQ-matched donors are available; 3) when matched donors are not available, limit the total number of HLA mismatches; 4) when selecting among HLA-mismatched donors, distinguish allele from antigen mismatches, and 5) consider KIR ligands, KIR alleles, and KIR haplotypes (presented in the following section).

Type and match at high resolution: The translation of polymerase chain reaction methodology to the field of histocompatibility paved the way for investigation into the clinical significance of HLA genetic variation. Beginning in the early 1990s, the field witnessed rapid dissemination of information on the importance of distinguishing unique alleles within serologically-defined antigen families, as risk factors for graft failure, GVHD and mortality [44-59]. These studies demonstrate that a single donor mismatch at either HLA-A, C, B or DRB1 increases the risk of GVHD after unrelated donor bone marrow transplantation with ablative conditioning; however, not all mismatches confer the same risks, and may result from different patient-donor HLA alleles due to ethnicity, to different transplant regimens, or other factors that influence transplant outcome. In an analysis by the CIBMTR for example, mismatching at HLA-B or C was less risky than mismatching at HLA-A or DRB1 [58]. Although a single HLA-DQB1 mismatch was not associated with higher GVHD risk, HLA-DQB1 mismatching together with mismatching at HLA-A, C, B or DRB1 significantly increased risks [58]. Data from these studies have collectively led to the establishment of HLA matching guidelines for the selection of unrelated donors for bone marrow transplantation [60].

Do the same principles of HLA mismatching in unrelated donor bone marrow transplantation also apply to transplantation of growth factor-mobilized peripheral blood stem cells (PBSCs)? A recent study by the CIBMTR found that any single mismatch at HLA-A, C, B or DRB1 (“7/8”) was associated with inferior outcome compared to 8/8 matching [61]. Among all mismatches, donor HLA-C antigen mismatching was associated with the worse outcomes compared to HLA-A, B or DRB1 mismatching. Furthermore, mismatching for HLA-C antigens but not HLA-C alleles increased the risk of grades III – IV acute GVHD and mortality, and lowered DFS. Emerging data in reduced intensity unrelated donor transplantation point to similarly detrimental effects of HLA-C mismatching on grades III-IV acute GVHD, non-relapse mortality and lower survival compared to matched HCT [56]. These data suggest that the criteria for the selection of mismatched donors may not necessarily be the same for PBSC as for marrow sources and indicate that more information is needed to clarify locus-specific risks between the two graft sources, intensity of the conditioning regimen, and GVHD prophylaxis regimens.

Consider HLA-DP: HLA-DP is a classical transplantation locus [62-71]. Mismatching for one DPB1 allele increases the risk of GVHD, and the effect is amplified with two DPB1 mismatches [66]. Among HLA-A, C, B, DRB1, DQB1-matched transplant pairs, only 15 – 20% are also HLA-DPB1-matched because of weak linkage disequilibrium (LD) between HLA-DP and the telomeric segment of the MHC. Considering that the identification of HLA-DPB1-matched donors requires extensive typing of a pool of HLA-A, C, B, DRB1, DQB1-matched ("10/10") donors, studies have focused on using *in vitro* cytotoxicity assays to identify specific T-cell epitopes (TCE) of patient-donor HLA-DPB1 mismatches that do not increase GVHD risk ("permissible mismatches") [68]. The TCE concept of matching for HLA-DPB1 has been validated in HLA-matched as well as HLA-mismatched unrelated donor transplantation [72]. Permissive HLA-DPB1 mismatches in HLA-A, C, B, DRB1 or DQB1-mismatched transplants have outcomes that are similar to those after HLA 10/10 matched non-permissive HLA-DPB1 mismatches. These data suggest that prospective evaluation and selection of selection of unrelated donors with TCE permissive HLA-DPB1 mismatches may lower the risk of GVHD after HLA-A, C, B, DRB1, DQB1-matched and mismatched transplantation.

How to select among mismatched donors: Although mismatching at each HLA locus increases risks, studies to date have yielded heterogeneous results with respect to the *relative* impact of mismatching among loci [49;58;61;73;74]. The relative risks between HLA-A, C, B, DRB1, DQB1, DPB1 mismatches are important when no HLA-matched donor is available, and transplantation from a mismatched donor is considered. Nevertheless, several important concepts have emerged from the international experience: 1) the negative effects of HLA mismatching are additive to one another; 2) HLA-DQB1 locus mismatches are the least risky, except when they occur in combination with mismatching at other HLA loci; 3) HLA-C antigen mismatches are highly deleterious, and 4) mismatching at certain epitopes are risky.

Limit the total number of HLA mismatches: The risk of GVHD increases as the number of HLA mismatches increases [45;47-49;51-54;58]. In particular, when one of the mismatches involves HLA-C, risks are especially high [53;58]. Although beneficial graft-versus-leukemia effects are observed, multi-locus mismatching with HLA-C is associated with poor survival rates [55;58].

Single DQB1 mismatches are better tolerated than single HLA-A, C, B or DRB1 mismatches: A single HLA-DQB1 mismatch is better tolerated than a single mismatch at HLA-A, C, B or DRB1 [53;58]. These data indicate that when HLA-A, C, B, DRB1, DQB1-matched donors are not available, donors with a single HLA-DQB1 mismatch might be considered.

HLA-C antigen mismatches are more risky than HLA-C allele mismatches: In unrelated donor bone marrow transplantation, an allele mismatch is just as deleterious as an antigen mismatch at HLA-A, B, or DRB1 but an HLA-C allele mismatch is better tolerated than an HLA-C antigen mismatch [58] . Similar relationships between HLA-C allele and antigen mismatches and transplant outcome are apparent after PBSC transplantation [61]. Although the absolute magnitude of risks conferred by HLA-A, C, B, DRB1 and DQB1 mismatches differ from study to study, donor mismatching at HLA-C has consistently been shown to be a risk factor after myeloablative and non-myeloablative transplantation using unrelated bone marrow, PBSC and cord blood units.

Mismatching at specific HLA epitopes is associated with increased GVHD: HLA mismatches do not contribute equally to GVHD risk. Patient-donor mismatching at residue 116 of HLA-B was one of the first epitopes to be identified with increased risk of acute

GVHD and TRM [75]. More recently, Tyr9–Phe9 of HLA-A and Tyr9–Ser9, Asn77–Ser77, Lys80–Asn80, Tyr99–Phe99, Leu116–Ser116, and Arg156–Leu156 of HLA-C were identified as critical epitopes associated with higher risk of GVHD among mismatches observed in the Japanese transplant population [76;77]. These data suggest that risks are not the same for every HLA mismatch, but depend on the specific residues that are mismatched for the particular combination of alleles or antigens. In turn, allele and antigen mismatches reflect the ethnic background of the transplant patient and donor. Parallel efforts are in progress to apply statistical and structural modelling to identify (non)permissive HLA mismatches [78-81].

2. Cord Blood Transplantation: In unrelated donor transplantation, GVHD risk is related to the total number of mismatches. In cord blood transplantation, there is strong evidence that fewer mismatches is associated with overall improved outcome, and that HLA-associated effects are influenced by the cell dose of the cord blood unit(s). Like unrelated donor HCT, there is emerging evidence that matching the cord blood unit for HLA-C will lower post-transplant complications. An important role for non-inherited maternal antigens (NIMA) provides an additional approach for lowering GVHD risk in cord blood transplantation.

Which loci should be typed and at what resolution: The current standard for HLA typing and selection of cord blood units is serological-equivalent level (low resolution) definition of HLA-A and HLA-B, and allele-level (high resolution) typing of HLA-DRB1 (a total of 6 determinants for a “6/6” match) [82;83]. Typing for HLA-A and B at the low resolution serological-equivalent level may be performed using either serology or DNA-based laboratory methods. Based on 6 HLA determinants, in most studies increasing the total number of HLA mismatches correlates with an increase in the risk of acute GVHD [82;84-90] but not chronic GVHD [84;88]. Compared to 6/6 matched transplants, the total number of mismatches at which a step-up of risk of acute GVHD is observed may be as few as 1 (“5/6”) [84] or 2 (“4/6”) [89], and furthermore, risks may depend on the specific combination of loci that are mismatched, ie, class I plus class II [85]. Differences between studies on the total number and nature of HLA mismatches that are most closely associated with both acute GVHD and survival, may depend on many additional factors including the underlying disease diagnosis (malignant or benign), the age of the patient (pediatric or adult), the conditioning regimen (ablative or reduced-intensity) and the cell dose of the cord blood unit (described below) [84;88;89;91;92]

There is strong evidence that HLA-C plays an important role in clinical outcome after cord blood transplantation. In a population of 803 patients, TRM was higher after single HLA-C-mismatched cord blood transplantation (HR 3.97, P = 0.018) compared to HLA-A, B, C, DRB1-matched transplantation [90]. Risks were further increased with the combination of mismatching at HLA-C with either HLA-A, B or DRB1 (HR 1.7, P = 0.029) compared to HLA-C-matched but single locus HLA-A, B, or DRB1-mismatched transplantation. The risk of TRM increased with 2 (HR 3.27, P = 0.006), 3 (HR 3.34, P = 0.005) and 4 (HR 3.51, P = 0.006) HLA mismatches compared to fully matched transplants. These data suggest that typing and matching for HLA-C, and avoidance of multi-locus mismatching that includes HLA-C, may lower mortality after cord blood transplantation.

HLA-C participates in both T cell and NK pathways, as described more fully in the section below. HLA-C is a ligand for natural **k**iller **i**mmunoglobulin-like **r**eceptors, or KIR. KIR ligand incompatible cord blood transplants have improved DFS and overall survival and lower relapse, the effect of which may be more evident in patients with AML than with ALL [93]. In other studies, KIR ligand mismatching was associated with higher grades III-IV acute GVHD and TRM and poorer survival after reduced intensity conditioning but ligand

mismatching did not correlate with acute GVHD, TRM, relapse, or survival after ablative conditioning [94]. Whether the differences in outcomes can be attributed to demographic differences between transplant populations (disease and disease stage, conditioning regimens, number of cord blood units transfused) remains to be evaluated with a larger transplant experience. Collectively, these studies indicate a role for typing patients and cord blood units for HLA-C to specifically avoid multi-locus mismatches that involve HLA-C.

If mismatching for HLA-A and B at a serological-equivalent level is clinically meaningful, is there sufficient evidence to warrant high resolution matching? In a study of 122 transplant pairs typed at high resolution at both HLA-A and B, there was no association of allele mismatching and transplant outcomes, although the number of pairs within each match grade were limited [86].These results contrast with those from a COBLT analysis of 179 patients typed at high resolution at HLA-A, B and DRB1, where high resolution matching was associated with lower risk of acute GVHD and a trend towards better survival for patients with a high resolution 6/6 match, worse survival for patients with a 3/6 match, although the differences were not statistically significantly different. [89]. High resolution matching did not affect neutrophil or platelet engraftment. Until there is more extensive data on larger numbers of cord blood transplant populations, the clinical utility of high resolution matching for class I alleles remains to be defined.

The interplay between HLA and cell dose: Cell dose was identified very early in the field as the most important determinant of outcome [82]. The role of cell dose has been demonstrated in single unit cord blood transplantation for adults [95-97] and in double cord blood transplantation, where the sum of the 2 units yields comparable engraftment as the same cell dose in a single unit [85;98]. Given that cell dose and HLA matching independently influence clinical outcome, investigators hypothesized that a higher cell dose might overcome the negative effects of HLA mismatching. The earliest descriptions of this complex interplay of HLA and cell dose found that a median infused total nucleated cell (TNC) dose of 3.7×10^7/kg was associated with a higher probability of neutrophil and platelet recovery and improved survival, and that matching for HLA-A and B at low resolution and HLA-DRB1 at high resolution was also associated with improved engraftment and survival [99]. The number of nucleated and CD34+ cells infused and the number of HLA mismatches are independent risk factors for outcome [84;85;98]. Although the optimal cell dose for each additional HLA mismatch has not yet been determined [85], higher cell doses in the setting of a single HLA mismatch lead to comparable rates of engraftment as HLA matching [88]. TRM is increased with transplantation of units with a cell dose lower than 3×10^7/kg and 1 HLA mismatch, or with the infusion of 2 HLA mismatched units independent of the cell dose infused [88]. The protective effect of a high cell dose is most robust when there is limited degrees of HLA mismatching [88]. With complete HLA matching, survival is superior regardless of cell dose [100].

Because of the strong association of transplant outcome with disease, the interaction between HLA and cell dose has recently been examined for patients with malignancies separately from patients with non-malignant disorders [101]. Among patients with malignant diseases, the negative effects of HLA mismatching were partially nullified by higher cell doses with the exception of patients transplanted from highly mismatched units (3 – 4 mismatches). As the number of HLA mismatches increased, so did the time to engraftment and the risk of chronic GVHD; although chronic GVHD was higher, patients benefited from lower relapse, and had comparable survival and DFS as patients with fewer mismatches. Among patients with marrow failure syndromes, primary immunodeficiencies or hereditary metabolic disorders, those receiving units with cell doses higher than 3.5×10^7 TNC/kg at infusion had optimal outcome. HLA mismatching was associated with delayed engraftment, higher GVHD and TRM and lower survival. These HLA-associated risks were partially

nullified by increasing the cell dose. Based on these observations, a cell dose of > 3.5×10^7 TNC/kg for units with 2 or more HLA mismatches has been recommended.

Collectively, these retrospective studies demonstrate that HLA match grade is of paramount importance in the setting of low cell dose. These data have led to the current recommendations for the selection of cord blood units containing a minimum pre-cryopreserved TNC of 3×10^7/kg and prioritization of units with larger TNC if there is HLA mismatching [82;83;102]. When 1 unit is not available, the co-infusion of 2 unmanipulated units and application of expansion methods may be used to optimize cell dose [102-104]. Avoidance of more than 1 HLA mismatch between the 2 units and the patient may help in lowering post-transplant complications to the patient [82]. How these criteria will change in the future when HLA-C and other loci are taken into consideration, remain to be determined. Additional refinements the criteria for HLA matching and cell dose remain to be defined for pediatric and adult patients receiving ablative or reduced intensity conditioning regimens [105].

NIMA effects in cord blood transplantation: The MHC is inherited *en bloc* on chromosome 6 through Mendelian segregation. In this way, an individual inherits one paternal and one maternal copy of chromosome 6, and is haploidentical to each parent. The non-inherited maternal MHC haplotype contributes HLA antigens to which the cord blood is exposed; this two-way trafficking of HLA antigens may promote tolerance of the **n**on-**i**nherited **m**aternal **a**ntigens ("NIMA") by the immune system of the fetus. Early evidence supported the tolerizing effects of NIMAs in renal transplantation [106;107]. Subsequently, observations were made of lower risks of acute and chronic GVHD and mortality after haploidentical marrow transplantation from mother to child, in contrast to higher GVHD rates after transplantation from father to child [108-110]. These results supported the role of donor-specific suppression of T cell responses against NIMAs and immunizing effects of paternal antigens. The haploidentical transplant experience suggests that prospective typing of the mother of the stem cell donor can aid in the identification of NIMA-matched donors as a means to lower morbidity and mortality after transplantation.

In cord blood transplantation, the beneficial effect of NIMAs on the patient may arise when the cord blood unit's mother's non-inherited HLA antigen is matched with the patient. To illustrate, a mother has the HLA-A1,2 tissue type; the cord blood unit is HLA-A1,3 and the patient is HLA-A1,2. The cord blood unit is mismatched with the patient for an HLA-A3 (unit) versus HLA-A2 (patient). However, the mother's non-inherited antigen, HLA-A2, is matched with the patient's HLA-A2. The hypothesis is that in utero, the cord blood is tolerized to the non-inherited HLA-A2 maternal antigen; after transplantation, the tolerization of the HLA-A2 is associated with lower risk of GVHD in the patient.

Proof of principle has been established in cord blood transplantation [111]. In an analysis of 1,121 patients receiving single cord blood unit transplants, 1,059 pairs were mismatched for one or two antigens at HLA-A and/or B and/or DRB1. Of these transplants, 79 (7%) were NIMA-matched (the mismatched antigen(s) were shared between the transplant patient and the mother of the cord blood unit). Lower TRM was observed with NIMA-matched transplants compared to NIMA-mismatched transplants. Although a subsequent analysis did not observe the same protective effect of NIMA matching to NRM or mortality [112], most recently a beneficial effect of NIMA matching has been observed in HLA-mismatched single unit CBTs, confirming the original analysis by van Rood an colleagues in 2009 [113]. In this case-control study of 48 NIMA-matched and 116 NIMA-mismatched transplants, NIMA-matched and NIMA-mismatched transplants had similar neutrophil recovery, acute and chronic GVHD, and relapse. TRM was lower (RR 0.48, P = 0.05) and mortality was lower (RR 0.61, P = .04) after NIMA-matched compared to NIMA-mismatched cord blood

transplantation. These data have important implications to the selection of cord blood units. For patients with malignant disorders and a choice of units, selection of a unit whose maternal typing shows a NIMA match to the recipient may lower overall mortality risks to the patient. In the future, elucidation of the interplay between cell dose, HLA match and NIMA match status may offer new approaches for improving outcomes.

3. Haploidentical Related HCT: The beneficial NIMA effects in haploidentical transplantation has stimulated investigation into the clinical importance of the number of mismatches on the non-shared haplotype. In a multicenter retrospective study of 185 patients receiving T-replete marrow from first-degree relatives [114], increasing numbers of host-versus-graft (HVG) vector mismatches were accompanied by a trend towards lower relapse and improved event-free survival. There was also a higher incidence of graft failure with 3 or 4 antigen mismatches in HVG vector compared to less than 3 mismatches, but the difference was not statistically significant. Mismatching for class I antigens showed a trend for lower risk of relapse (P = 0.04), however class I graft-versus-host (GVH) vector mismatches were not associated with any other outcome parameter. Increasing numbers of class I antigen mismatches in the HVG vector was associated with lower risk of relapse (HR 0.55, P = 0.02), as were HLA-DRB1 mismatches in the GVH vector (HR 0.65, P = 0.04) which led to improved event-free survival (HR 0.62, P = 0.009). There were no significant associations between grades II-IV acute GVHD and the number of HLA mismatches (HR 0.89, P = 0.68 for 3 – 4 HLA mismatches versus fewer than 3 mismatches) and the number of HLA mismatches had no effect on event-free survival. These results suggest that outcome after haploidentical related donor transplantation is influenced by the cumulative effects of HLA mismatching on the non-shared HLA haplotype which include NIMA-matched antigens.

II. Natural Killer Immunoglobulin-Like Receptors and Ligands

HLA class I molecules participate in both T cell and NK-mediated immune responses and for this reason are of great interest in understanding the molecular basis of GVHD and relapse. There is substantial data on the role of ligand mismatching and missing ligands on transplant outcome [115-120]. More recently, information on KIR haplotype gene content and KIR receptor gene diversity shed new light on the importance of the innate immune system in hematopoietic cell transplantation and offer novel approaches for lowering the risks of GVHD and relapse.

Definition of KIR ligands and receptors—KIR receptors can have inhibitory or activating potential. HLA-C serves as a ligand for inhibitory KIR receptors (KIR2DL1, KIR2DL2, KIR2DL3), as well as selected activating receptors (KIR2DS1, KIR2DS4). The specificity of the HLA-C ligand-receptor interaction is governed by residues 77 and 80 of HLA-C [30], which forms the basis of the two-group classification scheme known as “C1” and “C2”. C1 ligands encode Ser at position 77 and Asn at position 80 and are recognized by inhibitory KIR2DL2 and KIR2DL3 receptors. C2 ligands encode Asn at position 77 and Lys at position 80 and are recognized by the KIR2DL1 receptor. With high-resolution typing of HLA-C alleles, patients' KIR ligands can be readily defined as C1,C1 homozygous, C2,C2 homozygous, or C1,C2 heterozygous. The HLA-Bw4 motif is encoded by select HLA-B and HLA-A molecules, and is a ligand for inhibitory KIR (KIR3DL1). High resolution typing of HLA-A and B is sufficient to determine whether the ligands are Bw4-positive or Bw4-negative. Therefore, when HLA-A, B and C typing information are evaluated together, the ligands for any patient fall into only 1 of 6 possible groups: C1,C1,Bw4-positive; C1,C1,Bw4-negative; C2,C2, Bw4-positive; C2,C2, Bw4-negative; C1,C2, Bw4-positive, and C1,C2,Bw4-negative. These 6 groups serve as the basis for evaluating the clinical importance of ligand mismatching and missing ligands on transplant outcome.

Ligand models: mismatching versus missing—HLA and KIR genes are encoded on chromosomes 6 and 19, respectively, and segregate independently. In HLA-matched transplantation, the patient and donor must be KIR ligand matched; however, the patient may lack a ligand for the donor's receptor. In HLA-mismatched transplantation, the patient and donor can be mismatched for their KIR ligands and the patient may also be missing ligands. These characteristics distinguish the two models of NK alloreactivity in transplantation.

The original observations from the Perugia group in HLA-mismatched haploidentical transplantation tested the ligand mismatch model [118]. In this model, KIR ligand mismatching was associated with improved survival, and absence of graft failure, acute GVHD and relapse; KIR ligand matching was associated with an increased incidence of graft failure, acute GVHD and relapse. The beneficial effect of ligand mismatching was more pronounced in patients with myeloid leukemia than in patients with lymphoid leukemia. Subsequent studies examined the effect of KIR ligand mismatching in unrelated donor and cord blood transplantation and led to heterogeneous results, most likely due to demographic differences in the populations, variable transplant regimens and GVHD prophylaxis regimens and limited numbers of patients [118;121-130]. In one of the largest analyses to date, 1,790 T-replete unrelated donor transplants were evaluated for the clinical impact of KIR ligand matching [74]. The risk of acute GVHD was increased with disparity for HLA-A, HLA-B, HLA-C, HLA-DPB1, and KIR ligand mismatching in the GVH vector. Mismatching for HLA-A, HLA-B, HLA-DQB1, and KIR ligand in the GVH vector increased mortality. This analysis demonstrated an important role for HLA-C, HLA-DPB1, and KIR ligand mismatching in GVHD vector on post-transplant relapse. As a whole, KIR ligand mismatching had adverse effects on acute GVHD and rejection and had no survival benefit for patients undergoing T-replete unrelated HCT. In cord blood transplantation, two studies reach different conclusions regarding the role of KIR ligand mismatching on transplant outcome [93;94]. Whereas patients mismatched for KIR ligands had higher transplant-related mortality due chiefly to higher rates of acute GVHD [94] an independent analysis found lower relapse rates and better survival associated with ligand mismatching, particularly for patients with AML [93]. These studies highlight the need for continued analysis of large, well-characterized populations.

In the missing ligand model, the lack of the appropriate HLA ligand in the patient for the donor KIR receptor triggers NK-mediated killing of the patient's target cells leading to the desirable effect of lowered relapse after HCT [127]. In an analysis of T-replete unrelated donor transplants [130], HLA-mismatched recipients who were homozygous for HLA-Bw6 and HLA-C KIR ligand groups had a lower risk of relapse; this beneficial effect was not present among HLA-matched recipients. A study of patients receiving T-replete allografts for acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), MDS, and CML demonstrated striking differences in 1 year survival based on presence of KIR and HLA mismatching [131]. Mismatched transplants had lower overall survival and event-free survival compared to the matched transplants, and patients mismatched for both HLA and KIR had higher relapse and TRM than patients with any other HLA/KIR combination. In a side-by-side analysis of the two models, Ruggeri confirmed the protective effect of mismatched ligand and not missing ligand on disease recurrence [132]. In a large analysis of patients transplanted from unrelated donors for the treatment of myeloid malignancies, patients with low-risk diseases (first complete remission of AML, first chronic phase of CML, early stage MDS), a beneficial effect of missing ligand on lowered disease recurrence was readily apparent in both HLA-matched and HLA-mismatched transplants [133]. The protective effect was diminished in patients with more advanced disease.

Receptors—KIR genes are highly organized into haplotypes defined as “group A” and “group B” [30;134-140]. Whereas group A haplotypes encode primarily inhibitory receptors and the activating KIR2DS4 gene, group B haplotypes are more diverse and encode more activating genes including KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5 and KIR3DS1.

New information on the clinical relevance of KIR haplotypes and haplotype gene content provides insight into the relationship between ligand and receptor structure and function [141-145]. A dose effect for the number of donor B haplotypes is evident [144;146;147]. A dose effect for the number of activating KIR genes impacts the risk of relapse and DFS [148]. Transplantation from donors with group A haplotypes or from donors with lower numbers of activating KIR genes, was associated with a lower risk of relapse and higher DFS for patients with AML or MDS recipients but not for patients with ALL. On the other hand, KIR ligand mismatching was associated with significantly higher TRM, lower overall survival, and lower DFS compared to ligand matching. These data suggest that both the HLA ligand and the donor KIR haplotype define transplant outcome.

Since B haplotypes are distinguished by their specific gene content, the clinical impact of B haplotypes might be related to the presence of certain genes (for example KIR2DS1 or KIR3DS1) and/or the absence of other genes (KIR2DL3). In a cohort of T-replete HLA matched or mismatched unrelated donor marrow transplants for AML, CML, MDS or ALL, increased numbers of donor copies of KIR3DS1 correlated with lowered risk of grades II – IV acute GVHD, TRM and mortality [145]. To determine whether the KIR3DS1-associated dose effects were directly the result of KIR3DS1 or were due to other haplotype-associated genes, outcomes were analysed for transplants from donors with the B haplotype compared to donors without any B haplotype. GVHD risk was lower in B haplotype-positive transplants, and the haplotype effect was weaker than the KIR3DS1 effect. The presence of the HLA-Bw4 epitope was an independent protective factor for GVHD. These results suggest that future approaches for lowering risks of GVHD may include selection of donors with higher numbers of the KIR3DS1 gene.

MICA: ligands for the activating NKG2D receptor—As described above, a role for a methionine at residue 129 of MICA may be protective against GVHD [37]. Clinical outcome may also be affected by patient-donor mismatching at MICA because MICA is polymorphic with over 84 recognized unique alleles (http://hla.alleles.org). Two studies have evaluated the role of mismatching for MICA genes and risk of acute GVHD [149;150]. MICA mismatching was associated with an increased risk of grades II-IV acute GVHD but not grades III-IV acute GVHD in both HLA 10/10 matched and HLA-mismatched transplants [149]. Notably, MICA mismatching correlated with grades II-IV acute GVHD of the gastrointestinal tract (35% versus 17%, P = 0.05) and was independent of HLA-B and C mismatches. Transplant outcome did not depend on the number of MICA*008 alleles, the most common allele in North American/European Caucasians. Based on these data, the authors hypothesized that expression of MICA on the surface of intestinal cells may interact with NK cells through the NKG2D receptor as well as with γδ and αβ T cells. In a separate study of 38 patients transplanted from HLA 12/12 matched unrelated donors, there was no evidence for a correlation between MICA mismatching and risk of GVHD [150]. Overall, MICA mismatching in the setting of 6 locus HLA matching was rare. There was a trend towards less acute GVHD if patients were MICA*008-positive (P = 0.07), and a suggestive trend for severe acute GVHD of the gastrointestinal tract among patients positive for a shared MICA residue encoded by MICA*004, 006, 009, 044, 049 alleles (P = 0.075). Because of the strong positive LD between HLA-B and MICA genes, further examination of an independent cohort of 1676 8/8 matched unrelated donor transplants was conducted to determine whether specific patient HLA-B alleles correlated with GVHD risk. There were no differences in GVHD risk based on linkage of HLA-B alleles to MICA. Unlike the

former analysis, these data do not support a role for MICA mismatching in acute GVHD of the GI tract, nor for an allele association of MICA with GVHD.

IV. Non-HLA Genes of Clinical Significance

A. Haplotypes as Markers of GVHD—HLA haplotypes are comprised of HLA genes and other loci that are physically linked on the same chromosomal strand. The MHC encodes over 300 genes, many of which have immune-related function [151]. Hence, matching transplant donors for the classical HLA loci represents a minority of the possible haplotype-linked candidate genes that could affect GVHD risk. MHC haplotypes are comprised of blocks or segments of highly conserved DNA sequences [152]. HLA haplotypes are conventionally defined by their HLA-A, C, B, DRB1 and DQB1 alleles and antigens; for example, the most frequently observed HLA haplotype in Western European populations is HLA-A1, C7, B8, DR3, DQ2 [153]. HLA haplotypes can be distinguished from one another at many levels of genetic diversity, including coding regions of complex genes such as HLA, non-coding forms of variation including microsatellite markers and simple biallelic single nucleotide polymorphisms (SNPs) [152;154-162]. A hallmark of the MHC is the strong positive long-range LD. The long-range nature of this LD means that some human haplotypes are conserved over 7 megabases in length [163]. The strength of LD across the MHC has served as an important basis for understanding the organization of genes on haplotypes and on the ancestry and the history of human populations [164-167].

Evidence for the existence of clinically relevant genes outside of the classical HLA loci was provided by studies that used laboratory methods to define the extent of patient-donor mismatching for blocks or segments of sequences of the MHC in transplant patients and donors [168;169]. This early experience provided the impetus to use microsatellite markers to map candidate transplantation determinants within the MHC. Two recent studies provide strong evidence that HLA haplotypes are associated with GVHD risk. A large retrospective analysis of Japanese transplants showed the remarkable degree to which Japanese patients and their HLA-matched unrelated donors share the same SNP polymorphisms over very long genetic distances of the MHC [163]. A high level of sequence identity between patients and their donors meant a very low frequency of SNP mismatching. Three major HLA haplotypes were identified in the Japanese transplant population. The presence of some haplotypes was associated with high risk of GVHD, whereas other haplotypes appeared to be protective. This study provided evidence for the role of non-HLA haplotype-associated variation in GVHD.

In contrast to the Japanese experience, North American Caucasian patients and donors have more haplotypic diversity [162]. Using a method to physically separate the 2 HLA haplotypes in HLA-matched patients and transplant donors, pairs with different HLA-A, B, DR linkage were identified [170]. Compared to patients with the same HLA-A,B,DR haplotypes as their HLA-matched unrelated donors, patients transplanted from HLA-matched donors with different HLA-A,B,DR haplotypes had significantly increased risk of grades III-IV acute GVHD, suggesting that haplotype-linked variation could be responsible for the step-up of risk [171]. If haplotypes encode untested genetic variants that influence GVHD risk, what approaches can be taken to identify those risk variants? Mapping the MHC for disease-associated variants can be accomplished using microsatellites and SNPs, as described below.

B. Tools for Querying the MHC

Microsatellites: Microsatellite markers were instrumental in the construction of the second-generation human genome map [172-174]. Over 400 microsatellites have been identified within a 3.8 megabase interval of the HLA region of which 241 are polymorphic and can be typed using highly accurate and reproducible methods [175-177]. Since microsatellites provide

information over great distances across the MHC, they provide information beyond what can be gleaned from typing individual HLA loci [168;178-180]. These studies underscore the clinical utility of microsatellite markers as a more comprehensive measure of compatibility between unrelated individuals [181]. Microsatellite markers were successfully used to identify TNF as a GVHD determinant in Japanese patients [182]. As described below, the association of microsatellite-defined TNF alleles with an increased risk of GVHD in Caucasian transplant patients and donors has been confirmed [183].

SNPs: Single nucleotide polymorphisms (SNPs) are the most abundant kind of inherited variation [184;185]. SNPs are biallelic and occur at a frequency of 1 in 10 to 1 in 1000 bp. Because of their stability, SNPs are attractive for mapping disease genes [186]. Formal comparison of the utility of microsatellite and SNP markers has been made [187] and SNP platforms have provided an unique tool for understanding HLA haplotype diversity and organization (http://www.sanger.ac.uk/HGP/Chr6?MHC). Although microsatellites are abundant, have high degrees of polymorphism, and are informative for HLA haplotypes, SNPs can be genotyped in a positive/negative assay system and thus are highly amenable to automation. Through the efforts of multiple international SNP consortia, invaluable SNP data are available to facilitate disease mapping (http://www.sanger.ac.uk; www.ncbi.nlm.nih.gov; www.hapmap.org; www.1000genomes.org). In the future, characterization of common and rare HLA haplotypes in ethnically diverse populations will provide an invaluable resource for mapping genes in disease [162].

C. Class III Region Genes and GVHD: Tumor Necrosis Factor and Heat Shock Protein—

Immune response genes and cytokines contribute to the acute GVHD “storm” and influence chronic GVHD [188-198]. Two genes reside within the MHC class III region, tumor necrosis factor (TNF) and heat shock protein (HSP), and are haplotype-linked determinants of GVHD.

Tumor Necrosis Factor: TNF-α is a pro-inflammatory cytokine that is produced by macrophages, monocytes, NK cells, and T cells. TNF-α can induce several events that are part and parcel of the inflammatory response of GVHD including apoptosis of tissues and increased expression of HLA proteins; furthermore, TNF-α is associated with increased expression of IL-1, IL-6 and IL-10 cytokines [199]. The TNF block is a high LD-region that includes 4 distinct genes: TNF-α, TNF-β (lymphocytoxin-α, LTA), leucocyte-specific transcript-1 (LST1) and allograft inflammatory factor (AIF) [152;200]. The TNF region is characterized by microsatellite polymorphisms [165;200-202]. One of the best studied variants is the TNF promoter SNP position -308 in which the A allele has been associated with higher serum levels of TNF in some studies [203]. The literature on TNF and acute GVHD risk is heterogeneous [69;191;204-211] and likely due to differences in demographic characteristics among the study populations (ethnicity, donor type, HLA match status, conditioning and GVHD prophylaxis regimens) as well as relative small sample sizes that limit statistical power. Two recent studies have investigated the TNF block [183;212]. Using microsatellites, the presence of the d4/d5 alleles were risk markers for mortality [183]. Patients transplanted from d4/d5-positive donors had lower survival rates than did patients transplanted from d4/d5-negative donors. Additive effects of HLA-DPB1 mismatching in TNF d4/d5-positive donors further lowered survival. The Japan Marrow Donor Program (JMDP) used a candidate SNP approach to examine the impact of the TNF-1031 SNP on risk of acute GVHD risk in 2 large cohorts of Japanese patients transplanted from HLA-matched or mismatched unrelated donors [212]. Patient-donor mismatching at the TNF-1031 SNP was associated with grade IV acute GVHD.

Heat Shock Protein (HSP) 70hom: The HSP70hom gene resides within the TNF-LTA block of the class III region. HSPs function as carrier molecules for immunogenic peptides presented by antigen-presenting cells to cytotoxic T cells [213] and may induce monocytes to produce cytokines [214]. An association between anti-HSP70 antibody levels and risk of GVHD has been described [215], as has the level of HSP70 expression and GVHD [216]. The E602K amino acid substitution of HSP70hom has been identified as a risk epitope [217]. Compared to patients with the AA genotype, patients without AA had a lower risk of acute GVHD and fewer toxic complications. Lower risk of any GVHD correlated with the presence of the DRB1*11 tissue type indicating a protective haplotypic effect. In the candidate SNP study by the JMDP [212], there was no association between HSP70hom and GVHD. Whether the differences in other haplotype-linked markers between Caucasian and Japanese populations can explain the different results of these studies, remains to be defined in the future with larger, side-by-side comparative analyses.

D. Mapping Novel Transplantation Determinants within the MHC—The availability of high-performance SNP arrays has permitted investigators to fully map the MHC for genes that cause disease. HLA matching of unrelated donors can lower risks of acute GVHD and mortality compared to HLA mismatching, but does not guarantee that the patient will not have life-threatening GVHD. To determine whether undetected HLA haplotype-linked variation contributes to post-transplant complications after HLA-matched unrelated donor transplantation, a recent analysis was performed using a discovery-validation study design [218]. A discovery population of 2,492 HLA-matched donor-recipient pairs was used to first determine whether identify MHC-resident SNPs associated with acute or chronic GVHD, relapse, DFS, TRM or survival. Among a panel of 1,120 SNPs, 8 SNPs met a $P < 0.01$ as candidate markers for transplant outcome. A validation cohort consisting of 1,713 patient-donor pairs was subsequently characterized for each of the 8 candidate SNPs identified through the discovery cohort. Of these 8 SNPs, 2 were found to be significantly associated with transplant outcome. The first SNP, rs887464, resides in the class I region in close proximity to the PSORS1C3 and POU5F1 gene complexes. Donor mismatching for host-versus-graft was associated with higher mortality compared to matching (HR 1.93, $P = 0.0006$). The second SNP, rs2281389, resides 2 kb from the HLA-DPB1 3′ untranslated region. Donor mismatching at this SNP was associated with significant risks for grades II-IV acute GVHD. To determine whether SNP matching could be used prospectively to lower the number of patients transplanted from rs2281389-mismatched donors, a retrospective study was conducted for patients who had at least 2 HLA-A, C, B, DRB1, DQB1-matched donors identified on their unrelated donor search. Among 230 patients, only 35 (15%) did not have any SNP-matched donor. Sixty-five (28%) patients had at least 1 SNP-matched donor, and 130 (57%) had more than one SNP-matched donor. These data demonstrate that patients who have HLA-matched donors will have SNP-matched donors and suggest that selection of donors with favorable SNP genetics might lower acute GVHD after HLA-matched unrelated donor transplantation.

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Practice Points

- High resolution typing of HLA-A, C, B, DRB1 and DQB1 genes is used for the selection of unrelated donors for transplantation.
- Single HLA-DQB1 mismatches may be the best tolerated mismatches in unrelated donor HCT.
- Two-locus mismatching is associated with high risk of post-transplant complications after unrelated donor transplantation.
- The permissivity of selected HLA mismatches may not necessarily be the same for bone marrow as for peripheral blood stem cell transplantation from unrelated donors.
- When multiple otherwise equivalent unrelated donors are available, consideration for permissive TCE-defined HLA-DPB1 mismatches may help to lower the risk of acute GVHD.
- Minimal criteria for the selection of cord blood units includes low to intermediate resolution of HLA-A and B, and high resolution of HLA-DRB1.
- Interactions between HLA mismatching and cell dose of the cord blood unit(s) are complex.
- Multiple HLA mismatches in cord blood units with low cell dose are a high-risk combination of factors that lower the success of cord blood transplantation.
- HLA-C is a transplantation determinant in cord blood transplantation.
- KIR genes and haplotypes have clinical significance in transplantation.

Research Agenda

- Definition of permissible HLA mismatches in a variety of transplant settings and for patients and donors of diverse ethnic backgrounds: unrelated, haploidentical, cord blood transplantation; myeloablative, reduced-intensity, non-myleoablative conditioning; T-replete and T cell-depleted regimens.
- Elucidation of the clinical importance of KIR haplotypes and KIR gene diversity.
- Delineation of novel MHC resident gene variation that contribute to GVHD risk.