Blood Reviews 27 (2013) 1–12

Contents lists available at SciVerse ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Genetics of graft-versus-host disease: The major histocompatibility complex

Effie W. Petersdorf *

Division of Clinical Research, Fred Hutchinson Cancer Research Center, 1120 Fairview Ave N, Seattle, WA 98109, United States

ARTICLE INFO

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)

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.

1. 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.

2. 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 2013 HLA-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.

2.1. 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 2500 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.

2.1.1. 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

* Tel.: +1 206 667 5244; fax: +1 206 667 5255.
E-mail address: epetersd@fhcrc.org.

0268-960X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.blre.2012.10.001

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 1204 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 7950 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.

2.1.2. 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 a 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.

2.2. 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.

2.2.1. 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).

2.2.1.1. 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]