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In Celebration of Ruggero Ceppellini: HLA in Transplantation

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Abstract

The availability of hematopoietic cell transplantation as curative therapy for blood disorders has been dramatically improved through a better understanding of the HLA barrier. Although a fully compatible unrelated donor is preferable, transplantation from donors with a limited degree of HLA mismatching is associated with acceptable outcomes in many cases. Research on the limits of HLA mismatching, and the features that define permissible HLA mismatches will continue to enable transplantation to be more broadly available to patients in need.

Keywords

HLA; hematopoietic cell transplantation; unrelated donor; haplotype; expression; matching

The field of hematopoietic cell transplantation celebrated a landmark achievement in 2012 with the transplantation of the one millionth patient by the worldwide community.¹ Today, patients with life-threatening malignant and non-malignant blood disorders have a life-prolonging if not curative therapy, through allogeneic transplantation. To appreciate the significance of the clinical advancements that have led to this remarkable milestone, one must acknowledge the development of effective conditioning regimens, improved drug regimens to prevent and treat graft-versus-host disease (GVHD), advancements in the supportive care of transplant recipients, and the establishment of volunteer donor registries.^{2–5} These clinical advancements have been feasible with the concurrent landmark discoveries by pioneers in the HLA field that permitted the safe transplantation of tissues from an allogeneic source.^{6–11} Each year at the annual meeting of the European Federation for Immunogenetics, The Ceppellini Lecture is presented to honor Ruggero Ceppellini (Figure 1). It is a great privilege to recognize the scientist, the teacher and the pioneer who first put forward the concept of the linkage of transplantation antigens on haplotypes, for it is this contribution that paved the way for the development of allogeneic stem cell sources as curative therapies for patients, and has furthered understanding of the clinical significance of haplotype-associated genetic variation.

In June, 1967, Ruggero Ceppellini chaired the third International Histocompatibility Workshop in Turin, Italy, where investigators established the correlations between specificities encoded by genes at a single chromosomal locus. At the workshop, Ruggero

Ceppellini noted that "... a new term can be introduced without increasing confusion, it is suggested to substitute pheno-group with haplotype ... in fact, the name should convey the concept that the haplotype is not an observed phene and corresponds to the product of a single gene dose".¹² The concept that HLA specificities were the products of closely-linked genes, served as the genetic starting point for the development and refinement of the stem cell transplantation procedure using relatives who share one HLA haplotype with the recipient^{13–14} and for understanding the importance of MHC region variation.^{15–17}

In the absence of a genotypically-identical related donor, the use of well-matched unrelated donors can offer life-saving transplantation. A major barrier to successful transplantation remains acute and chronic GVHD, second only to disease recurrence as a major cause of transplant failure.¹⁸ The most effective approach for lowering the risks of GVHD is through prospective donor HLA matching.^{19–22} Yet, the likelihood of identifying well-matched donors can be a significant bottleneck particularly for patients with less common allotypes and haplotypes. In the United States, patients of non-Caucasian background may have a particular challenge in identifying a suitable donor for transplantation. For example, 16% of patients of African-American background have HLA-A, B, C, DRB1 (8/8)-matched donors, but the odds increase substantially to over 79% when donors with a single HLA (7/8) mismatch are considered.²³ Contributing to the challenge of donor matching are two factors: the polymorphism of the HLA system, and the size and composition of unrelated donor registries.⁴ As of December, 2016, there are over 3657 HLA-A, 4459 HLA-B, 3290 HLA-C, 1977 HLA-DRB1, 978 HLA-DQB1 and 716 HLA-DPB1 alleles currently recognized.²⁴ The strong positive linkage disequilibrium (LD) both helps and hinders the identification of matched donors. For example, matching for A*01:01 and B*08:01 greatly increases the probability of matching for DRB1*03:01 for Caucasian recipients and donors; however, when the recipient has inherited less frequent haplotypes those odds depend heavily on the combination of alleles at HLA-A,C,B,DRB1, and the allele and haplotype frequencies in registry donors.^{25,26} Mismatching at HLA-B may increase the chance of mismatching at HLA-C; the same LD exists between HLA-DRB1 and DQB1. A major research focus has been to better understand the limits of HLA incompatibility: which mismatched loci confer the highest risks, what combinations of multi-locus mismatches are detrimental, and which non-HLA factors should be considered in donor selection. Major advances in the field of HLA have shed light on the allele, antigen and locus-specific risks, wherein GVHD, relapse and mortality may depend on the number of amino acid substitutions between the donor and recipient's mismatched HLA allotypes, the position of the mismatched residue, the nature of the substitution, and most recently, the level of expression of the recipient's mismatched HLA.

In 1979, an interesting clinical observation was made wherein recipients of HLA-identical sibling transplants who developed acute GVHD had, on the whole, lower overall rates of disease recurrence compared to patients who did not experience clinical GVHD.²⁷ The hypothesis that donor T-cells could mount an anti-recipient alloresponse against disparate minor histocompatibility recipient antigens, including residual host leukemic blasts that survive the conditioning regimen, was confirmed in several series^{28–30} and gave rise to the term "graft-versus-leukemia" effect (GVLE). HLA mismatching is generally associated with higher risks to transplant recipients; a beneficial effect of GVHD-associated HLA

mismatching has been observed for some but not all HLA loci. Recently, an analysis by the JMDP demonstrated that each HLA mismatch does not necessarily confer the same beneficial GVL effect.²¹ Side-by-side analysis of donor-recipient mismatching at each HLA locus uncovered a beneficial lowering of relapse associated with mismatching at only HLA-C and HLA-DPB1. These observations strongly suggest that future investigation into the underlying mechanisms responsible for GVL involving T and/or natural killer cell-mediated effects will facilitate understanding of GVLE in transplantation.

Number and nature of mismatched HLA residues

The biological implications of HLA sequence diversity have been amply demonstrated in the setting of unrelated donor and cord blood transplantation.^{19–21,31} The earliest reports of single amino acid differences between the class I allotypes of the transplant recipient and donor identified residues 116 and 156 of HLA-B as risk factors.^{32–33} In the unrelated donor transplant experience, the advent of molecular methods for tissue typing provided an important tool for understanding the implications of HLA-C sequence polymorphisms on graft failure.³⁴ In a single center study of patients receiving unrelated donor grafts for the treatment of chronic myeloid leukemia following myeloablative conditioning, the risk of primary graft failure correlated strongly with the number of HLA-C mismatches as defined by molecular typing methods.³⁴ No graft failure was observed among patients with a single HLA-C allele-defined disparity in contrast to patients with one serologically-defined HLA-C antigen mismatch. The HLA-C antigen mismatches were characterized by multiple disparities at key residues that influence the peptide binding repertoire and/or residues that contact the T-cell receptor.

More recently, donor-recipient mismatching at specific HLA-C residues mismatches has been shown to increase the risk of GVHD and mortality, and lower the risk of disease recurrence.^{35–37} In a large retrospective analysis from the Japan Marrow Donor Program (JMDP), donor-recipient mismatching for Tyr9Ser, Tyr99Phe, Leu116Ser or Arg156Leu was associated with a significantly increase risk of acute GVHD.³⁵ The importance of mismatching at residue 116 of class I on mortality was validated by the Center for International Blood and Marrow Transplant Research (CIBMTR) wherein the risk of mortality was 1.8 times that of matching at residue 116.³⁷ Donor anti-host alloresponses may also be driven by natural killer (NK) cells where HLA-C allotypes as defined by residues 77/80 serve as ligands for inhibitory receptors.³⁸ There is now substantial evidence for a role for activating and inhibitory NK receptors and their cognate class I ligands in transplant outcome.^{39–41} KIR2DL1/KIR2DL2/KIR2DL3 ligand mismatching is associated with graft rejection⁴² and KIR2SD1 Group 2 ligands (Asn77/Lys80) with disease recurrence after transplantation.⁴³ These studies collectively support the role of class I peptide repertoire and NK-mediated class I pathways in clinical outcomes and the potential to leverage the beneficial recognition of host tumor cells to lower disease recurrence.⁴⁴

HLA-DP: A lesson in T-cell epitopes

HLA-DP is a classical transplantation antigen. Donor-recipient mismatching is associated with a higher risk of acute GVHD and lower relapse indicative of GVLE.⁴⁵ The effect of

HLA-DP disparity is dose-dependent,⁴⁶ such that mismatching for two HLA-DP allotypes is accompanied by higher risks than mismatching for one allotype. The delineation of six “hypervariable” regions that define the peptide-binding region within the polymorphic exon 2 of HLA-DPB1 provides a starting point for exploring the role of T-cell epitopes (TCEs) in GVH and GVL responses.⁴⁷ In early studies, tolerance to shared alloreactive TCEs could be predicted by the strength of cytotoxicity of HLA-DP-directed T cell clones that were originally recovered from a transplant patient.⁴⁸ Three major groups of HLA-DP allotypes could be discerned, correlating with high, intermediate and low levels of cytotoxicity. The degree of *in vitro* alloreactivity was informative for defining pairwise HLA-DP allotype combinations that could be predicted to be associated with higher (non-permissive) or lower (permissive) risk of GVHD and mortality.⁴⁹ Importantly, independent validation in two separate cohorts demonstrated that donor-recipient HLA-DP permissive mismatches can be used safely when no HLA-DP-matched donors are available.^{50–51} To further investigate the molecular basis of TCE reactivity, mutational studies of key amino acid residues were performed and the impact of these changes were measured relative to a consensus allele; a functional distance score reflects a measurement between TCE-defined groups and mutated amino acid positions, and correlates with (non)permissive HLA-DPB1 mismatches.^{52,53} With knowledge of the recipient and donor’s HLA-DPB1 alleles, any given donor-recipient HLA-DPB1 mismatch can be readily predicted to be permissive or non-permissive based on established risks. A robust clinical tool has been developed to aid the selection of donors with permissive HLA-DP-mismatches.²⁴

HLA expression: a new model for identifying permissive HLA mismatches

The low-expression HLA-DRB3, DRB4, DRB5 loci are not routinely considered in prospective donor selection; however, their role in GVHD is evident particularly when the recipient and donor have a known HLA-A, B, C or DRB1 mismatch.⁵⁴ Formal proof for a role for HLA expression in GVHD and mortality risks has been provided for HLA-C and DP. In the case of HLA-DP, the identification of regulatory region variation responsible for expression was feasible through fine mapping studies of the MHC. Those fine mapping studies tested the hypothesis that undetected MHC variation may contribute to GVHD and mortality after HLA-matched unrelated donor transplantation. One of the most powerful approaches for locating disease-associated variation is through the use of single nucleotide polymorphism (SNP) surveys. SNPs are informative for narrowing the genetic regions that are most likely to encode disease-associated variants. SNPs are cost-effective to genotype and easy to interpret. SNPs that are in strong positive linkage disequilibrium (LD) with other genetic variants (tagSNPs) provide information for untyped SNPs and serve as proxies for genes that cause disease. In a retrospective analysis of HLA-matched unrelated donor transplants, a tagSNP survey of the MHC yielded candidate markers associated with clinical outcome.¹⁶ Use of an independent validation cohort facilitated the identification of a class I region SNP that correlated with mortality and a class II region SNP that associated with GVHD risk. Of interest, the class II marker resides in a non-coding region and is in strong positive LD with polymorphisms within the HLA-DPB1 genetic locus including the 3’ regulatory region of the gene. Fine mapping of the rs9277534 regulatory region variant and its correlation with HLA-DP expression (as measured by quantitative [q]PCR), identified

haplotypes of HLA-DP allotypes and the rs9277534 A or G alleles.⁵⁵ In a retrospective study of patients who received HLA-matched unrelated donor transplants with a single HLA-DPB1 disparity, mismatched recipient HLA-DP allotypes linked to rs9277534A (low HLA-DP expression) were associated with significantly lower risk of GVHD compared to mismatched recipient allotypes linked to rs9277534G (high HLA-DP expression). When the rs9277534-linked HLA-DP allotypes were compared to TCE-defined groups, overlap in TCE permissive mismatches with rs9277534A low-expression recipient HLA-DP allotypes was observed, as was overlap in TCE-defined non-permissive mismatches with rs9277534G high-expression recipient allotypes. Among TCE-defined HLA-DP mismatches, rs9277534 provided additional information on risks of GVHD, suggesting that the level of expression of HLA-DP in the recipient is an important prognostic indicator of donor-anti-host recognition. Future studies that define epitope and expression features of HLA-DP mismatch combinations will help elucidate the immunogenicity of key residues presented by high and low-expression allotypes. Together with new data on HLA-DP expression levels in the control of hepatitis B infection,⁵⁶ non-coding region variation has direct consequences on the immunogenicity of HLA-DP allotypes.

The level of expression of HLA-C allotypes has recently been a focus of investigation in the HIV and autoimmunity models.^{57,58} Higher HLA-C expression is protective against HIV-AIDs progression, whereas low HLA-C expression is protective in Crohn's disease. In hematopoietic cell transplantation, the level of HLA-C expression was evaluated as a risk factor for GVHD after single HLA-C mismatched unrelated donor transplants.⁵⁹ To test the hypothesis that increasing levels of expression of the recipient's mismatched HLA-C allotype is associated with increasing risk of acute GVHD, patients and their HLA-C mismatched donors were retrospectively evaluated using established allotype-specific mean fluorescence intensity (MFI) levels as a basis for allotype-specific expression.⁵⁷ As the level of MFI of the patient's mismatched HLA-C allotype increased, the risks of grades III – IV acute GVHD and non-relapse mortality also increased, suggesting that higher expression alloantigens in the recipient are potent targets for donor-anti-host recognition.⁵⁹ Given the importance of residue 116 of HLA-C in GVHD and residues 77/80 in defining HLA-C C1/C2 KIR ligands, the risks of GVHD and mortality were analyzed for patients with low-expression and high-expression HLA-C mismatches according to the presence of residue 116 mismatching and the presence of KIR ligand mismatching. Compared to low-expression residue 116-matched transplants, the risks of GVHD and mortality in low-expression residue 116-mismatched and high-expression residue 116-matched transplants were similar; however, the risks were significantly increased in the setting of high-expression residue 116 mismatching. Likewise, risks were similarly low for low-expression KIR ligand-matched, low-expression KIR ligand-mismatched and high-expression KIR ligand-matched transplants, but significantly increased for high-expression KIR ligand-mismatched patients. These observations strongly suggest complex synergistic effects of HLA expression, residue mismatching and KIR ligand mismatching on transplant outcomes.

Conclusions

The practice of hematopoietic cell transplantation has led to a dramatic increase in cure rates for blood cancers. Advances in understanding the HLA genetic barrier have extended this

life-saving therapy for patients who lack related donors. As Ruggero Ceppellini predicted 50 years ago, “for the practical purpose of clinical transplantation it is, however, important to evaluate the efficiency of HL-A typing for selecting the best unrelated (cadaver) donor”, could not have been more clairvoyant.⁷ For patients who lack matched donors, the use of donors with selected HLA mismatches has increased the availability of unrelated donor transplantation. The features of mismatched HLA allotypes that contribute to post-transplant risks include mismatching at key class I and HLA-DP residues that define the peptide-binding repertoire, and the nature of the class I KIR ligand. A role for HLA-C and DP expression in GVH allorecognition highlights the biologic consequences of non-coding region variation and the utility of non-coding variation in defining permissible HLA mismatches. The identification of non-HLA MHC haplotype-associated variation has been made possible with the advent of SNP mapping tools that provide an unprecedented view of MHC sequence diversity. The critical premise for the use of genetic markers to locate genes that cause disease, is the notion that haplotype-linked markers are proxies for one another. In this way, Ruggero Ceppellini’s legacy is the foundation of modern disease-association mapping.

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Figure 1.
Ruggero Ceppellini (1917 – 1988), pioneer, teacher, and Chairman of the 3rd International HLA Workshop, 1967, Turin, Italy. Photographs courtesy of Prof. Antonio Amoroso.