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REVIEW

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Human leucocyte antigen diversity: A biological gift to escape infections, no longer a barrier for haploidentical Hemopoietic Stem Cell Transplantation

Marco Andreani[1] | Stefania Gaspari[2] | Franco Locatelli[2]

[1]Laboratorio d'Immunogenetica dei Trapianti, Polo di Ricerca di San Paolo, Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

[2]Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

Correspondence
Marco Andreani, Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica, Laboratorio d'Immunogenetica dei Trapianti, Polo di Ricerca di San Paolo, IRCCS Ospedale Pediatrico Bambino Gesù, Viale Ferdinando Baldelli 38, 00146 Roma, Italy.
Email: marco.andreani@opbg.net

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Abstract

Since the beginning of life, every multicellular organism appeared to have a complex innate immune system although the adaptive immune system, centred on lymphocytes bearing antigen receptors generated by somatic recombination, arose in jawed fish approximately 500 million years ago. The major histocompatibility complex MHC, named the Human leucocyte antigen (HLA) system in humans, represents a vital function structure in the organism by presenting pathogen-derived peptides to T cells as the main initial step of the adaptive immune response. The huge level of polymorphism observed in HLA genes definitely reflects selection, favouring heterozygosity at the individual or population level, in a pathogen-rich environment, although many are located in introns or in exons that do not code for the antigen-biding site of the HLA. Over the past three decades, the extent of allelic diversity at HLA loci has been well characterized using high-resolution HLA-DNA typing and the number of new HLA alleles, produced through next-generation sequencing methods, is even more rapidly increasing. The level of the HLA system polymorphism represents an obstacle to the search of potential compatible donors for patients affected by haematological disease proposed for a hematopoietic stem cell transplant (HSCT). Data reported in literature clearly show that antigenic and/or allelic mismatches between related or unrelated donors and patients influences the successful HSCT outcome. However, the recent development of the new transplant strategy based on the choice of haploidentical donors for HSCT is questioning the role of HLA compatibility, since the great HLA disparities present do not worsen the overall clinical outcome. Nowadays, NGS has contributed to define at allelic levels the HLA polymorphism and solve potential ambiguities. However, HLA functions and tissue typing probably need to be further investigated in the next future, to understand the reasons why in haploidentical transplants the presence of a whole mismatch haplotype between donors and recipients, both the survival rate and the incidence of acute GvHD or graft rejection are similar to those reported for unrelated HSCTs.

KEYWORDS
Hemopoietic Stem Cell Transplantation, HLA, polymorphism, population studies

1 | HLA POLYMORPHISM DEVELOPMENT OVER TIME

When life began on our planet more than 3.5 billion years ago, every multicellular organism appeared to have a complex innate immune system although evolution suggests that the adaptive immune system (AIS) emerged in mammals, arising approximately 500 million years ago, in jawed fish (Cooper & Alder, 2006; Flajnik, 2018; Flajnik & Kasahara, 2010; Hirano, Das, Guo, & Cooper, 2011; Stringer, 2016). Two macro evolutionary events are supposed to have contributed to the genesis of the AIS: the emergence of the recombination-activating gene transposon and two rounds of whole-genome duplication. The major histocompatibility complex (MHC), present only in vertebrates, is probably from the so-called MHC big bang that produced a duplication of an ancestral gene in a paralogous one. Three MHC-like paralogous regions, sharing a large number of similar genes, are present in humans. The duplication of a "proto MHC" region overcame the functional limitations allowing the evolution into the modern MHC (Abi Rached, McDermott, & Pontarotti, 1999; Flajnik, 2014).

Genetic data indicate that approximately 45,000–60,000 years ago, a very rapid population expansion occurred outside Africa, across the Eurasian continents, populating the entire world. It was, however, not until about 40,000 years ago that anatomically modern humans, *Homo sapiens sapiens*, emerged (Henna et al., 2012).

Certainly also due to migration and to infection susceptibility, the polymorphism of MHC in humans strongly developed over time, with the characteristic to produce a large amount of allelic variations for each of the human leucocyte antigen (HLA) genes. It is interesting to note that in other species, such as in rhesus macaques, many region configurations were present, but with lower allelic variations and higher haplotype distribution (de Groot et al., 2015; de Groot et al., 2016). In a recent paper, Robinson et al. examined, individually and/or in combination, the variation in exons 2 and 3 of HLA-A, HLA-B and HLA-C in more than 10.000 class I alleles using a new developed multisequence dot-plot analysis. They showed that HLA-C alleles diverged amongst themselves to a lesser extent than HLA-A or HLA-B alleles but also that HLA-B and HLA-C were more closely related to each other than to HLA-A. They suggested that HLA-A and HLA-B are million years older than HLA-C and that this last originated from a duplication of an HLA-B allele. Moreover, they also showed nucleotide substitutions present in more than 95% of the positions for all the three genes analysed, producing an amino acid variation for each of the alpha 1 and 2 domain positions. Interestingly, more than 84% of them were determined in rare alleles (Robinson et al., 2017).

In 1954, when Dausset first described the first HLA gene, which he named MAC (an acronym made up of the initials of the first three donors with whom the serum he was testing did not react), he probably did not perceive the complexity of the MHC and in particular the extensive level of polymorphism of the whole system (Dausset, 1954). From the MAC discovery, subsequently named HLA-A*02, more than 500 subtypes of that allele have been defined, by sequencing exons 2 and 3, which encode for the polymorphic antigen-binding site of HLA class I (Parham, 2018). In total, based on international ImMunoGeneTics (IMGT) data, by September 2018, sequences for more than 18.000 HLA class I and II alleles were deposited in the database. The biological and clinical relevance of the HLA system has been deeply studied in the recent years. It is involved in defence versus infections, in transplantation activities, in autoimmunity and in pregnancy but also largely contributed to the understanding of the different populations' diversity, providing information relative to their history, to their migration and to their susceptibility and/or resistance to different diseases.

Population data were collected in large HLA databases to count or estimate the number of existing alleles. Besides the IMGT®, known as the international ImMunoGeneTics information system®, the Gene[VA] database of the HLA-net platform, maintained at the University of Geneva and the Allelefrequencies.net (AFND), maintained at the University of Liverpool, are the most known (Abraham et al., 2018; Gonzalez-Galarza et al., 2018; Nunes et al., 2014). These tools allow the analysis of HLA data in human populations, such as the allele and haplotype frequencies estimation, or testing the Hardy–Weinberg equilibrium. Moreover, they are helpful for testing selective neutrality and linkage disequilibrium to display population frequencies of chosen alleles and haplotypes in selected geographic regions or to perform genetic comparisons amongst chosen sets of population samples, including new data provided by the users.

On the other hand, common and well-documented (CWD) HLA allele catalogs were recently developed. It is interesting to observe that 50% of the CWD alleles reported in the European Federation for Immunogenetics (EFI) catalog differ from those published by Mack et al., underlining the distinct features of the ethnicity investigated (Mack et al., 2013; Sanchez-Mazas, Nunes, et al., 2017). These catalogs, including the one recently published by a German group (Eberhard, Schmidt, Mytilineos, Fleischhauer, & Müller, 2018), once again document how the worldwide genetic variation in HLA is characterized by specific geography differences, suggesting that probably natural selection alone did not cover the signatures of human migration history.

On the other hand, many different reports have been published in literature, showing HLA polymorphisms amongst specific populations. Sanchez-Mazas et al., for example, recently determined the signatures of pathogen-driven selection in Africa, studying the polymorphism of HLA-A and HLA-B loci in a large number of individuals from 11 populations, living in different environments, across the Sahel, comparing the data with 29 other African populations (Sanchez-Mazas, Černý, et al., 2017). The results confirmed a highly significant association, conferring protection, of allele B*53 with malaria prevalence, but also of alleles B*78 and A*74. They also showed that in all the B*53-positive individuals identified, this allele was present almost exclusively as B*53:01:01, with the only exception of one case, in which a rare B*53:19 allele was found in a small seminomadic population. The study demonstrated once again that pathogen-driven selection modelled the HLA genetic patterns, shaping several HLA allele frequency variations across Africa, in addition to populations' demography and migration history.

2 | HLA POLYMORPHISM AND HSCT

In the scientific community, it is well accepted that the success of allogeneic HSCT transplantation improves with the extent of HLA matching between donor and recipient. In particular, it has been shown that antigenic and/or allelic mismatches between donor and recipient in exon 2 and 3 for HLA class I and exon 2 for HLA class II strongly influence the HSCT outcome. Many authors have published different contributions in the literature focusing on this issue, trying to define which specific antigen and/or allele mismatches might mostly influence the hazard ratios for overall survival (OS), acute graft-versus-host disease (aGvHD) or graft rejection (Lee et al., 2007; Petersdorf et al., 2004; Petersdorf et al., 2013).

A work from Kekre et al. recently summarized the relevance of the donor recipient matching, showing a better survival in the 10/10 matched pairs respect to the 9/10 mismatched in a meta-analysis, relative to 13.446 Marrow Unrelated Donors (MUDs) HSCT cases, collected in 13 different published independent studies (Kekre et al. 2016). In particular, the data showed that mismatches at HLA-A, HLA-B, or HLA-C were statistically significantly associated with a lower overall survival. On the other hand, no significant difference was observed with -DQ or -DPB1 mismatches, whilst an inferior survival was associated with HLA-DRB1 mismatch although not statistically significant.

In a recent study, De Santis et al. investigated if matching outside of the antigen recognition sites (ARS) or matching for additional HLA genes further improve the outcome of HSCT in a group of 267 adult patients affected by malignant haematological diseases. They retrospectively typed with next-generation sequencing (NGS) at 3 or 4 fields the HLA of the donor and of the patients. They showed that polymorphisms outside the ARS may be markers of specific haplotypes and that matching for these polymorphisms improves the clinical outcome of HSCT (De Santis 2019).

Several approaches for characterizing differential alloreactivity amongst HLA mismatches have been suggested to improve clinical outcome in HSCT. Amongst these matching for the amino acid at position-116; compatibility between KIR ligands on donor and recipient cells expressing HLA-B and HLA-C antigens for evaluating NK cell alloreactivity; cell surface expression levels of HLA-C alleles or cytotoxic T-cell precursor (CTLp) frequency assay have been examined. (Davies et al., 2002; Pidala et al., 2013, Petersdorf et al., 2004, Israeli et al., 2014). These studies have contributed to the improvement of clinical outcome after HSCT, although the choice to determine the best-mismatched unrelated donor is still to certain extent controversial.

3 | PERMISSIVE HLA POLYMORPHISM AND HSCT

To improve the clinical outcomes in HSCT, many studies recently focused their attention on the possibility to individuate permissive HLA mismatches between donor and recipient. A good example is represented by the C*03:03/C*03:04 mismatched HLA allele combination, observed in a survey of 7,349 patients treated with HSCT described by Fernadez-Vina et al. Authors showed that the presence of this particular HLA-C allele mismatch is tolerated, with lower risks of acute aGvHD and higher survival rates than other HLA mismatches (Fernandez-Viña et al., 2014).

The possibility to identify permissive HLA mismatches for HSCT outcomes was recently investigated by Lazaryan et al. based on the similarities present both in predicted structure and function of the epitope binding grooves of HLA molecules. They categorized single mismatched alleles into six HLA-A (A01, A01A03, A01A24, A02, A03, A24), six HLA-B (B07, B08, B27, B44, B58, B62), two HLA-C (C1, C2) and five HLA-DRB1 (DR1, DR3, DR4, DR5, DR9) supertypes. They showed that supertype B07, B44 mismatch was associated with a higher incidence of both grade II-IV and III-IV acute aGvHD whilst no significant associations were identified between supertype-matched versus supertype-mismatched groups at other HLA loci (Lazaryan et al., 2016).

Although not validated in other surveys, very interesting are the results published by Kawase et al., relative to a Japanese population of transplant patients, showing how different specific combinations of donor and recipient HLA-mismatched alleles ended up permissive (Kawase et al., 2007). The authors analysed 5,210 donor/recipient pairs treated with HSCT that were all retrospectively typed for HLA-A, HLA-B, HLA-C, -DRB1, -DQB1, and -DPB1 alleles. Fifteen different high-risk HLA allele mismatched combinations and one HLA-DRB1-DQB1 linked mismatched combinations correlated with occurrence of aGvHD. They also identified six different amino acid substitutions, located in positions 9, 77, 80, 99, 116 and 156 in HLA class I molecule associated with the presence of aGvHD (Kawase et al., 2007).

Crocchiolo et al. proposed an algorithm to identify permissive HLA-DPB1 disparities (Crocchiolo et al., 2009). Based on cross reactivity pattern, DPB1 alleles were classified by the authors into three groups with high, intermediate or low immunogenic potential defined by the presence of T-cell epitope (TCE) mismatches between donor and recipient. HLA-DPB1-allele mismatches are therefore considered as permissive if the mismatched alleles belong to the same group and nonpermissive if they belong to different groups. Petersdorf et al., with a completely different approach, showed that the HLA-DPB1 rs9277534 expression marker influenced the risk of GVHD occurring in patients transplanted with a HLA-DPB1 mismatched donor (Petersdorf, Malkki, O'hUigin, Carrington, Gooley, Haagenson, 2015). Nevertheless, it was interesting to observe that except one, all the other DPB1 alleles included in the immunogenic T-cell epitope groups 1 and 2 described by Crocchiolo and Fleishhauer were present in the haplotypes containing the gene rs9277534G, associated with high HLA-DP expression (Fleischhauer, 2015). On the contrary, the most frequent alleles from the poorly immunogenic T-cell epitope group 3 were linked to the rs9277534A-containing haplotype that is associated with low HLA-DP expression.

Arrieta-Bolaños et al. recently successfully demonstrated the relevance of an in silico model based on the numerical functional distance (FD) characterizing T-cell epitope (TCE) to evaluate the impact of permissive or nonpermissive DPB1 mismatches on the clinical outcome after unrelated HSCT. In 2,730 transplant

patients for haematological diseases, they showed that nonpermissive mismatches evaluated with both traditional TCE algorithm and TCE-FD scores were associated with reduced overall survival (Arrieta-Bolaños et al., 2018).

In an attempt to determine satisfying HLA mismatched combinations, when no genotypically identical siblings are suitable and there are alternative potential donors for HSCT, an interesting tool is represented by HistoCheck. This algorithm evaluates the amino acid differences between pairs of HLA alleles, indicating their exchange positions and suggesting if these positions can be assigned to the peptide binding site or eventually to regions that might have a contact with the T-cell receptor. (Elsner & Blasczyk 2002; Elsner et al., 2004). However, Histocheck results, evaluated in large clinical study, did not always correlate with clinical outcomes (Spellman et al., 2012).

Geneugelijk et al. recently described a new informatics tool, which is supposed to predict indirect T-cell recognition, called predicted indirectly recognizable HLA epitopes (PIRCHE) (Geneugelijk et al., 2014; Geneugelijk & Spierings 2018; Geneugelijk et al., 2019), representing a new emerging approach to determine satisfying HLA-mismatched combinations for the choice of unrelated HSCT donor. PIRCHE is an algorithm that predicts which peptides amongst the HLA mismatched molecules can be presented by the shared HLA molecules of the patient and of the donor. PIRCHE identifies mismatched HLA-derived epitopes presented by both HLA class I and HLA class II molecules: PIRCHE-I and PIRCHE-II, respectively. Contrary to other models, PIRCHE predicts indirect T-cell recognition but not direct. In a recent study relative to a Dutch multicenter cohort of 103 patients, treated with HSCT from a single HLA-mismatched unrelated donor, Geneugelijk et al. showed that a high PIRCHE-II score had a significantly impaired OS compared with a low PIRCHE-II score and to a group of 10/10 matched pairs.

4 | HAPLOIDENTICAL HSCT

The availability of a 10/10 or 9/10 matched HLA donor, eventually characterized by the presence of a permissive mismatch, has been considered until very recently, when a favourable condition emerged for proposing HSCT to patients affected by haematological diseases, both in related and unrelated settings. However, despite the large HLA antigenic disparities present on the cells of a haploidentical donor, impressive clinical results have been obtained, both in paediatric and adult patients, with no detrimental effects on the successfully outcome of the HSCT. Therefore, the recent development of transplant strategies based on the choice of haploidentical donors for HSCT is changing the point of view relative to the role of the HLA in HSCT, moving the focus of histocompatibility and immunogenetics on different directions, probably towards a better understanding of the whole HLA haplotype characteristics and roles.

It is well-known that HLA haplotypes, first described by Ceppellini et al. in the sixties, are inherited as blocks (Ceppellini et al., 1967) where many different SNPs are, as well as the HLA loci, present in strong linkage disequilibrium. Recent studies by Petersdorf et al. have shown how the influence of noncoding variations might be one of the keys to understanding the level of expression of HLA genes and therefore of the HLA functions on alloreactivity in MUD transplantation (Petersdorf & O'hUigin 2019). However, the reason why the presence of many HLA antigenic and allelic mismatches present in a transplanted completely different donor haplotype does not determine evident detrimental clinical results in the haploidentical HSCT settings represents a relevant issue that future studies will need to investigate deeper.

Haploidentical HSCT was mainly developed to offer an opportunity of treatment virtually to any patient lacking an HLA 10/10 allelic matched donor, whether sibling or unrelated. Different approaches and clinical protocols have been developed to perform haploidentical transplants over the last few years, including T-cell depletion (TCD), either complete or partial; T-cell replete (TCR), performed using post-transplant cyclophosphamide GvHD prophylaxis; or G-CSF-primed bone marrow graft and enhanced GVHD prophylaxis (Sidlik-Muskatel & Reisner 2019).

The role of natural killer (NK) cells has been shown to be relevant in the haploidentical settings. NKs play a role in innate defences against viruses and tumour cells, mainly due to the sophisticated and wise use of their activating and inhibitory killer immunoglobulin-like receptors (KIRs) and CD94/NKG2A. Due to their ability to recognize and bind HLA class I molecules through these receptors, NKs know how to discriminate between normal, infected or malignant cells. This potential alloreactivity action was considered extremely useful in the choice of the donor in the HLA haploidentical settings for high-risk acute leukaemia transplant patients. Donor-derived NK cells, expressing inhibitory specific KIR for self-HLA class I alleles (KIR-ligand), will in fact be able to eliminate the patients' cells missing the same HLA class I ligand.

The group of Perugia first introduced the use of highly purified T-depleted CD34 positive cells in haploidentical settings, isolated either from bone marrow or peripheral blood, after a myeloablative conditioning regimen, in acute leukaemia patients, leading to sustained engraftment and GvHD prevention, without the need for any post-transplant immunosuppressive treatment. Ruggeri et al. reported a 5-year survival probability of 60% in adult AML patients in the case of donor NK alloreactivity (KIR/KIR-L mismatch in graft vs. host direction), whilst survival was <5% in its absence (Aversa, Tabilio, Velardi, CunninghamI, & Falzetti, 1998; Ruggeri et al., 2002).

The occurrence of early relapses and infections, mostly due to delayed NK cell reconstitution, led Locatelli et al. to develop a novel approach for haploidentical HSCT(Locatelli et al., 2013). They introduced a full myeloablative preparative regimen, based on the negative depletion of αβ-T and B cells, using anti–T-lymphocyte globulin from day 25 to 23 for preventing graft rejection and graft-versus-host disease (GVHD) with any post-transplantation GVHD prophylaxis. (Bertaina et al., 2014; Locatelli et al., 2018; Locatelli et al., 2017). In a survey of 80 consecutive paediatric patients affected by acute leukaemia and transplanted with a haploidentical donor after αβT- and B-cell depletion, the leukaemia-free survival (LFS) probability was 70.7% after 5 years. Comparing the clinical outcome with consecutive patients transplanted in the same centre in a similar period, relative to 41 HLA identical related

and 51 10/10 allelic matched unrelated HSCT, Locatelli showed an LFS of 65.7% and 68.1%, respectively (Bertaina et al., 2018). In comparison with other studies mainly based on infusion of CD34 + cells, this study did not document any favourable influence of NK cell alloreactivity and of donor KIR B haplotype. Using this approach, the NK-mediated GVL effect is partially concealed by other immune effector cells present in the graft, such as γδT cells (Bertaina et al., 2017).

Alternatively, different groups introduced the use of T-cell replete nonmyeloablative conditioning regimens in conjunction with cyclophosphamide (Cy) treatment post-transplant. A retrospective study by McCyrdy et al. analysed 684 adults with haematological malignancies who received T-cell replete bone marrow grafts and Cy after myeloablative HLA-matched related (n = 192) or unrelated (n = 120), or nonmyeloablative HLA-haploidentical (n = 372) donor transplantation. In multivariable models, authors did not find statistically significant differences in GvHD, relapse-free survival after either myeloablative HLA-matched unrelated or nonmyeloablative HLA-haploidentical, compared with myeloablative HLA-matched related donor transplantation (McCurdy et al., 2017).

Gaziev et al. showed that in survey of patients affected by hemoglobinopathies the use of TCRαβ+/CD19+ depleted grafts was associated with significantly reduced graft failure, compared to patients with hemoglobinopathies treated with CD34+ selected haploidentical cells (Gaziev et al., 2018).

Based on the data reported in the literature, it looks clear that the high degree of HLA-mismatch, both antigenic and/or allelic on the not shared haplotype does not seem to play a role in the selection of the best haploidentical donor. Kasamon et al. reported that combining high-dose of Cy and post-grafting immunosuppression in a nonmyeloablative T-cell replete BMT treatment for haploidentical HSCT, greater HLA disparity did not worsen the overall outcome (Kasamon et al., 2010).

To investigate if a PIRCHE high score might be helpful in predicting transplant success, Hou et al. investigated its role in a group of 577 patients affected by haematological disorders and receiving haploidentical HSCT. The authors concluded that in the observed survey, PIRCHE score did not correlate with clinical outcomes and could not predict better success in the haploidentical transplant settings (Huo et al., 2018).

On the other hand, the presence of anti-HLA immunization of the patients seems to represent a relevant negative risk to systematically observe before performing haploidentical HSCT (Fuchs 2012; Ciurea et al. 2015). In a recent study, Yoshihara et al. observed a strong association between primary graft failure and the presence of DSAs in a survey of 122 patients treated with T-cell-depleted or T-cell-repleted in haploidentical transplants (Yoshihara et al., 2012). At this purpose, to harmonize clinical activity, the European Society for Blood and Marrow Transplantation (EBMT) recently released recommendations for donor selection for haplo-HSCT considering the several different approaches to this kind of transplant (Ciurea et al., 2011; Ciurea et al., 2019). Amongst these, for a recipient with DSAs is considered relevant the choice of a donor without corresponding HLA antigen. Moreover, younger donors should be chosen over older donors, besides consider NK cell alloreactive donors, if available, when T-cell depleted transplants are performed.

5 | CONCLUSIONS

Recent years have demonstrated how the number of HLA-haploidentical hematopoietic cell transplants continues to successfully increase worldwide over time despite the presence of the numerous HLA antigenic mismatches present in the full-unshared haplotype. On a certain point of view, daily efforts to determine the allelic resolution of each HLA gene based on NGS routine activity seems frustrated by the excellent clinical results produced by the haplo-nonidentical donors for HSCT to treat blood disorders. Actually, either many studies have reported the presence of a greater number of HLA mismatches at the antigen or allele level in different large surveys, this did not worsen the overall outcomes concerning GVHD, relapse and NRM in haploidentical HSCT settings compared to unrelated HSCT.

The next few years will indicate if the haploidentical HSCTs will remain an alternative source when a HLA identical sibling or an unrelated donor will not be available, or if they will become the first transplant choice, considering the immediate availability of potential donors and the success already reported in the literature. Moreover, the scientific experience carried out by the haploidentical HSCT will hopefully clarify the impact of specific HLA antigens/alleles mismatches or perhaps contribute to answer to the question regarding the utility of matching at a structural respect to a functional level.

CONFLICT OF INTEREST

Authors do not have any conlfict of interest.

ETHICAL APPROVAL

The review did not require any ethical approval.

ORCID

Marco Andreani https://orcid.org/0000-0003-3451-3624

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