Chapter 1

Immunogenetics of Hematopoietic Stem Cell Transplantation

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1. Introduction

There are few hematopoietic stem cells (HSCs) in the bone marrow of adult mammals; these are required throughout life to replenish the short-lived mature blood cells of specific hematopoietic lineages. HSCs have several biological functions including homeostasis control, regeneration, immune function and response to microorganisms and inflammation.

The regenerative potential of human HSCs is best illustrated by successful stem cell transplantation in patients with a variety of genetic disorders, acquired states of bone marrow failure and cancer [1].

The first bone marrow transplantation took place in 1949 with studies that demonstrated the protection provided to the spleen of mice given a dose of irradiation that would otherwise be lethal. In 1960, studies in dogs provided important information about bone marrow transplantation in exogamic species, results that are applicable to humans. It was demonstrated that dogs could bear 2-3 times the lethal dose of total body irradiation with an infusion of bone marrow cells collected and cryopreserved before irradiation [2,3].

At the same time that animal experiments were being carried out, a number of attempts were made to treat humans with chemotherapy or irradiation associated with bone marrow infusions [4].

The first successful allogeneic bone marrow graft was achieved in a patient with leukemia, although the patient died due to the complications of chronic graft-versus-host disease (GVHD) [5].

Currently, bone marrow transplantation is the treatment of choice for many hematologic diseases with the course of transplant being dependent on several factors, including the stage of the disease at transplant, the conditioning regimen, source of cells, genetic factors, and the development of GVHD. The goal to this chapter is to show some genetic factors that have a strong influence on hematopoietic stem cell transplantation (HSCT) outcomes, such as the genes of the human leukocyte antigen (HLA) system located in the major histocompatibility complex (MHC), and other genetic factors, including non-HLA genes that seem to influence transplant outcomes and that are being studied to optimize donor selection. Non-HLA genes mainly include killer cell immunoglobulin-like receptor (KIR) genes, cytokine genes and receptors, MHC class I-related chain (MIC) genes and human minor histocompatibility antigens (mHAgs).

2. HLA immunogenetics and its influence on hematopoietic stem cell transplantation

Histocompatibility

The immune system is the result of germline selection and thymic education (self vs. non-self) through contact with pathogenic life and is thus a characteristic that is unique to each individual and specific to a given point in time; like all other physiological systems, the immune system is affected by disease, stress, trauma and environmental events [6].

An important cell lineage within this system is represented by T lymphocytes. The main functions of T lymphocytes are defense against intracellular microorganisms and the activation of other cells including macrophages and B lymphocytes.

T lymphocytes are capable of interacting with other cells because the antigen receptors on T cells recognize antigens that are presented by other cells; presentation is achieved by specialized proteins that are encoded by genes in a MHC locus [7]. The MHC system has the greatest diversity of all functional genetic systems at the population level [6]. The MHC glycoprotein family, also referred to as HLAs, presents endogenous and exogenous antigens to T lymphocytes for recognition and response.

This system was discovered in mice by Peter Gorer and George Snell. These researchers discovered an antigen which was involved in tumour rejection and subsequently they showed that similar antigens in other strains of mice were probably alleles of the same "tumour-resistant" gene [8].

Experiments show that transplants of tissue between animals from the same population (endogamic) were successful, while the consequence of transplants between animals from different populations (exogamous) was the rejection of tissue. The result of these studies was the discovery of MHC genes which are capable of recognizing foreign antigens and presenting them to T lymphocytes.

Antibodies induced by transfusions or pregnancy and which react with leukocyte antigens were first recognized in 1954. Studies showed that kidney transplant patients who suffered

rejection have circulating antibodies reactive to antigens present in leukocytes; as these antigens are expressed on leukocytes they were named HLAs [9,7].

Many studies were conducted over the next few years to understand and characterize the immunogenicity of these antigens.

Structure and function

The MHC, contained within 4.2 Mbp of DNA on the short arm of chromosome 6 at 6p21.3, has more than 200 genes, most of which have functions related to immunity. It is divided into three main regions [10].

The HLA-A, -B and -C classic genes and -E, -F and -G non-classic genes, as well as other genes and pseudogenes are located in the HLA Class I region near to the telomere. The HLA Class II region, near to the centromere, contains the HLA-DR, -DQ and -DP genes. The HLA-DR sub-region, includes the DRA gene that encodes the alpha chain is non-polymorphic and can bind with any beta chain to encode for DRB genes [11].

Located between class I and II regions, the class III region has C2, C4A, C4B and B factor, that encode complement proteins and the tumour necrosis factor (TNF) [10,11].

HLA molecules are polymorphic membrane glycoproteins found on the surface of nearly all cells. Multiple genetic loci within the MHC encode these proteins with each individual simultaneously expressing several polymorphic forms from a large pool of alleles in the population. The overall structure of HLA class I and class II molecules is similar, with most of the polymorphisms found in the peptide binding groove (PBG) where antigens are recognized [12].

Class I molecules are made up of one heavy chain (45kD) encoded within the MHC and a light chain called β2- microglobulin (12kD) whose gene is on chromosome 15. Class II molecules consist of one α (34kD) and one β chain (30kD) both within the MHC [10]

The class I heavy chain has three domains with the membrane-distal α1 and α2 domains being polymorphic. Within these domains, polymorphisms concentrate in three regions: positions 62 to 83, 92 to 121, and 135 to 157. These areas are called hypervariable regions. The two polymorphic domains are encoded by exons 2 and 3 of the class I gene. Diversity in these domains is very important because these two domains form the antigen binding cleft or PBG of MHC class I molecules [13,14].

The sides of the antigen binding cleft are formed by α_1 and α_2, while the floor of the cleft is comprised of eight anti-parallel β sheets. The antigenic peptides of eight to ten amino acids (typically nonamers) bind to the cleft with low specificity but high stability. The α_3 domain contains a conserved seven amino acid loop (positions 223 to 229) which serves as a binding site for CD8 [12,15-17].

Class II molecules consist of two transmembrane glycoproteins, the α and β chains which are restricted to cells of the immune system (e.g. B cells, dendritic cells - DCs), but can be induced by other cell types during immune response. The PBG of class II molecules has

open ends which allow the peptide to extend beyond the groove at both ends and therefore to be longer (12-24 amino acids). The peptide is presented to CD4 T cells [10].

Generally both the α and β chains in class II molecules are polymorphic. In these chains, the $\alpha 1$ and $\beta 1$ domains are of the PBG and therefore the diversity is found mainly in these domains. These domains are encoded by exon 2 of their class II A or B genes and the hypervariable regions tend to be found in the walls of the groove [16].

T-cell activation occurs following recognition of peptide/MHC complexes on an antigen-presenting cell (APC). T-cell activation can be viewed as a series of intertwined steps, ultimately resulting in the ability to secrete cytokines, replicate and perform various effector functions. During antigen presentation, CD4 and CD8 are intimately associated with the T-cell receptor and bind to the MHC molecule. Besides this interaction between T cells and APCs, ligation between counter-receptors on the T cell and accessory molecules on the APC is required as additional signals for T-cell activation [18].

Haplotype, Linkage Disequilibrium and Expression of HLA genes

HLA genes are transmitted following Mendel's law of segregation, so the allelic variant is codominantly expressed. The set of alleles present in the HLA loci located in a single chromosome of a chromosome pair is called a haplotype. The probability that two siblings having the same HLA haplotype is 25%; in this situation, it is considered that they are matching [11].

Moreover, a fact called linkage disequilibrium occurs in HLA genes. This means that certain alleles occur together at a higher frequency than would normally be expected by chance (gametic association). Consequently, some combinations of alleles appear more or less commonly in a population than would normally be expected from a random formation of haplotypes from alleles based on their frequencies [10].

For example, if a determined population has genic frequencies of 14% and 9% for HLA-A*01 and HLA-B*08, respectively, the expected frequency of a haplotype with this combination would be 1.26% (0.14 x 0.09). However, the true frequency may be 8.8% in this population, that is, higher than expected, characterizing a positive linkage disequilibrium [11].

Examples can be seen in studies of linkage disequilibrium related to bone marrow donation. A strong linkage disequilibrium has been reported for HLA-B*39:13 with the DRB1*04:02, DRB1*08:07 and A*31:12 haplotypes in the Brazilian population [19].

Other reports for unrelated donors involved HLA-A*01 and HLA-B*08, HLA-A*03 and HLA-B*35 and HLA-A*02 and HLA-B*12. This type of results suggests that these data have clinical application, such as in the selection of unrelated donors for bone marrow transplantation [20].

HLA compatibility of donors

The genetic origin of patients for whom bone marrow transplantation has been proposed, is a key determinant in the possibility of identifying compatible unrelated and sibling donors and consequently in the possibility of performing the procedure.

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The strict HLA compatibility that is required for bone marrow transplantation increases the difficulties in finding donors. A patient has one chance in four of having a compatible donor among his brothers and sisters. This chance becomes one in a million, on average, in unrelated donors [21].

Different methods are used to identify HLA antigens. In the past, HLA antigens for bone marrow transplantation were identified by serological methods based in mixed lymphocyte culture. However this technique is not as sensitive as molecular biology methods which can define HLA antigens at the allele level.

In molecular analysis, HLA genes can be identified by polymerase chain reaction (PCR) using the Specific Sequence Primers (SSP), Specific Sequence Oligonucleotides (SSO) or sequencing techniques. These methods are the most commonly used due to its specificity and sensibility that can define HLA genes only (low resolution) or genes and alleles (high resolution).

These results are very important in bone marrow transplantation in order to choose the best matched donor. The probability of finding a well-matched unrelated donor is improved if high resolution typing is available for the patient prior to the search. Therefore typing must ideally be done by DNA methods to avoid hidden mismatches, particularly in the case of antigenically silent alleles, and should include the HLA-A, -B, -C and -DRB1 genes at least [10].

Matched or mismatched donors

There are many studies which try to show that better outcomes in bone marrow transplantation are linked to full donor matches. In 2004 the National Marrow Donor Program (NMDP) published the results on the outcomes of 1874 unrelated donor transplants. This study showed a highly significant survival advantage for 8/8 matched pairs compared to those with one or two mismatches [22].

Moreover, the study of the Center for International Blood and Marrow Transplant Research (CIBMTR) examined clinical outcomes in recipients of both sibling and unrelated donors for chronic myeloid leukemia (CML) in the first chronic phase. There were 1052 recipients of unrelated transplants; 531 were matched for 8/8 alleles, 252 mismatched for 1 (7/8) allele and 269 mismatched for multiple alleles [22]. The overall survival (OS) at 5 years was 55% for 8/8 matched transplant recipients, 40% for those with a 7/8 matched graft and 21-34% for those with various multiple mismatched combinations. The recipients of stem cell matched related donors, predominantly siblings, have lower risk of infections, of the reactivation of cytomegalovirus and of mortality than the latter group. Additionally, T-cell immunity reconstitution is delayed in mismatched sibling donors and the unrelated group [23, 24].

Graft rejection, GVHD and delayed immune recovery, the major obstacles to successful allogeneic HSCT, are more severe with unrelated donors than in HLA-identical sibling transplants. Because identical donors are available to only about 30% of patients, the identification of a suitable unrelated donor by better, more precise HLA matching of donor and recipient is necessary [25].

Studies have shown strong negative effects of HLA mismatching of the HLA-A, -B, -C, -DRB1 or -DQB1 loci on OS. The presence of multiple mismatches was worse for survival and for severe acute GVHD (grade III-IV). Other trials analyzed the incidence of chronic GVHD in patients who survived more than 100 days after transplantation. It became evident that a HLA-A/B mismatch induces a significantly higher incidence of chronic GVHD and lower OS rate. The same was not confirmed for a HLA-DQ/DR mismatch that showed no association with the occurrence of chronic GVHD [25;26].

High resolution HLA typing can help in the characterization of donors; there are differences in the outcomes of bone marrow transplantation if the mismatching of donors was defined by low or high resolution. Studies show that high resolution matching of HLA-A, -B, -C and -DRB1 between volunteer HSC donors and recipients is associated with a better survival. Additionally, single HLA-B and -C mismatches appear to be better tolerated than single HLA-A or -DRB1 mismatches [27].

Other studies affirm that survival after unrelated HSCT for severe acquired aplastic anemia has improved significantly over the last 15 years mainly due to better HLA matching at the allelic level [28].

HLA and bone marrow transplantation

The outcome of transplantation using unrelated donors is highly influenced by HLA matching between the donor and recipient. Two particular individuals always differ in their genome structure in respect to minor histocompatibility antigens, killer cell immunoglobulin-like receptor (KIR) genes and several other groups of genes.

However, the most potent transplantation antigens are the HLAs encoded by genes located in the MHC. HLA-C is a class I gene locus, yet its importance in transplantation has been less validated than the HLA-A and B loci [10].

However, studies that analyzed structure and peptide-binding for HLA-C, show that divergence in peptide-binding specificity may be a contributor to the risk of mortality after transplantation perhaps due to the alloreactivity of donor T cells towards peptides presented by patient HLA molecules but not by donor antigens presenting cells during T-cell development in the thymus [29].

There are two main reasons for the HLA antibodies to result in graft failure and GVHD. The first is the rapid increase in the number of HLA-mismatched HSCT, including in cord blood transplantation, haploidentical HSCT and unrelated HSCT. The second is the technical advance in the methods of HLA Ab testing, which have attained a rapid, accurate and objective identification and qualification of specific HLA antibodies [30].

HLA, sibling and unrelated hematopoietic stem cell transplantation

Matched or mismatched

The use of stem cells from HLA-matched unrelated volunteer donors is an accepted option for patients without a matching sibling donor providing comparable outcomes to matched sibling donor HSCT. Many studies have been performed to compare the results between sib-

ling and unrelated transplantation. Other studies show single results about sibling and unrelated transplantation, the importance of HLA compatibility and what effect HLA mismatches may have on GVHD, graft failure and relapse.

Research has shown that HLA class II DRB1*15 (*15:01 and *15:02) are important in the outcome to sibling matched transplants for patients who have aplastic anemia. In multivariate analysis, the secondary graft failure rate at two years was lower in patients who were HLA-DR15+[31].

Recent studies in a Chinese population show that the outcome of unrelated donor transplantation matched for HLA-A, HLA-B and HLA-DRB1 but unknown for HLA-C antigens was associated with a significant risk of mortality and that this risk was higher with HLA-A, B or DRB1 mismatches compared to an 8/8 match [32].

Other studies confirm that there is no association between HLA mismatching of unrelated donors with the cumulative incidence of grade II-IV or grade III-IV acute GVHD. Similarly, there was no association with chronic GVHD, but the incidence of graft failure was higher in HLA-mismatched unrelated transplants [33]. Trials highlight the importance of defining HLA by high resolution techniques to improve the outcomes in pediatric transplants using unrelated donors. The patients that suffered graft failure were mismatched for HLA-C by a high resolution technique [34].

However, studies show that in unrelated transplantations, the outcome is improved when the patients are HLA-C and HLA-DPB1 mismatched in some combinations, thus resulting in lower risk of relapse. Probably some combinations increase the graft-versus-leukemia (GvL) effect [35].

One study analyzed the impact of HLA class I and II high-resolution matching of 1874 unrelated donors and found that HLA-C mismatching was most strongly associated with graft failure, HLA-A mismatching was associated with significantly increased risk of grade III/IV acute and chronic GVHD and mismatches of HLA-A, B, C and DR were associated with death [36].

HLA and Haploidentical HSCT

When no matched sibling or unrelated donor exists, the potential curative option is haplo-HSCT, that is, transplant with a donor who shares only one haplotype with the recipient. Haploidentical stem cell transplants are increasingly used in the treatment of malignancies, and immune and hematologic diseases. As multiple mismatched related donors may be available for transplantation, it is important to select a donor that is most likely to produce a successful outcome [37].

There are studies that correlate the HLA-B mismatch effect in haplo-HSCT. Studies analyzed the impact of HLA-A, -B, -DRB1, -DRB3, -DRB4 and -DRB5 and demonstrated that a HLA-B mismatch not only has a significant effect on GVHD and transplant-related mortality but was also associated with reduced OS and leukemia-free-survival [38].

There is an important point in haploidentical transplants that should be considered: the conditioning regimen. Many protocols have been performed to improve the outcomes of trans-

plantation and to minimize the effect of HLA incompatibility. For example, studies on nonmyeloablative HLA-haploidentical bone marrow transplantation with high-dose post-transplant cyclophosphamide. The results showed that HLA mismatch was not associated with relapse or GVHD [39].

In bone marrow transplantation with mismatch of the HLA-DRB1 antigen in the GVHD direction and two or more HLA Class I (HLA-A, -B and -Cw) mismatches in either direction were found to be associated with decreased incidences of relapse without an increased incidence in nonmyeloablative conditioning with post-transplant cyclophosphamide [40].

HLA and cord blood transplantation

The use of umbilical cord blood transplantation (UCBT) for patients with hematological malignances or hereditary diseases is becoming increasingly more common. In October 2006, the International NETCORD Foundation maintained an inventory of more than 124,000 umbilical cord blood (UCB) units and documented more than 4900 unrelated UCBT [41]. Several studies have shown that the number of cells is the most important factor for engraftment, while some degree of HLA mismatch is acceptable.

For example, studies show that unrelated UCBT is comparable to a 1-antigen mismatch at the HLA-A, HLA-B or HLA-DR loci in respect to GVHD, relapse and OS [42]. For other studies on UCBT, HLA-A and -B are defined by low-resolution and HLA-DRB1 by high-resolution, with minimum compatibility of 4/6. It is important to apply the rules of equivalence of serological groups for HLA-B*14, -B*15, -B*40, and -B*50 as determined by molecular methods [43].

Clinical comparison studies of UCBT and HLA-A, -B and -DRB1 6/6 allele-matched bone marrow transplantation or single mismatched for leukemia from unrelated donors in adult recipients showed similar results. There was no significant increase of relapse rates among UCB recipients when compared with DRB1 single-mismatched bone marrow recipients. The OS for UCB recipients was similar too when compared with DRB1 single-mismatched bone marrow recipients [44].

Korean pediatric studies also show that the results of UCBT are promising. One study compared the outcomes of acute leukemia children submitted to transplantation using UCB, bone marrow and peripheral blood stem cells from HLA-matched or unrelated donors. The results confirm that survival after UCBT was similar to survival after matched related donor and unrelated donor transplantations. In conclusion, for patients lacking an HLA matched donor, the use of UCB is a suitable alternative [45].

Additionally, studies show that recipients of UCB transplants from HLA-identical siblings have lower incidences of acute and chronic GVHD than recipients of bone marrow transplants from HLA-identical siblings [46]. Hence, studies on the distribution of HLA alleles and haplotypes in different ethnic populations are also important to find a suitable unrelated cord blood donor for a patient. One study investigated the frequencies of alleles and HLA-A, -B and -DRB1 haplotypes with high-resolution typing data in a total of 710 Taiwanese UCB units [47]. The most common alleles found for HLA-A were

A*11:01, A*24:02, A*33:03 and A*02:01; for HLA-B they were B*40:01, B*46:01, B*58:01 and B*13:01 and for DRB1 they were DRB1*09:01, DRB1*12:02, DRB1*15:01 and DRB1*03:01. Moreover, the five most frequently found haplotypes were A*11:01, B*35:05, DRB1*11:02; A*24:07, B*35:05, DRB1*12:02; A*01:01, B*5701, DRB1*09:01; A*11:01, B*40:01, DRB1*09:01 and A*11:01, B*46:01, DRB1*09:01. These haplotypes are common in Taiwanese and Asian American populations [47].

Ethnic studies carried out in London showed that the most common alleles in 1500 UCB units were HLA-A*34, A*36, A*80, HLA-B*75, B*61, B*53, B*78, B*81 and B*82. This kind of study should help to increase the chances of obtaining acceptably HLA-matched donors for patients from ethnic minorities [48].

3. Non-HLA immunogenetics and its influence on hematopoietic stem cell transplantation

Natural killer cells and Killer immunoglobulin-like receptors

Human natural killer (NK) cells are components of the innate immune response that comprise approximately 10-15% of all peripheral blood lymphocytes and play a major role in immunity against viral infections and tumors [49-51]. Years of intensive research in mice and humans have shown a special importance of NK cells in the hematological diseases and in mediating favorable HSCT outcomes [52-57]. NK cells were first identified by their *in vitro* capacity to kill tumor cells without the requirement of prior immune sensitization of the host [58-59].

The function of NK cells is regulated by a diverse array of cell-surface receptors including KIR, NKG2D and DNAM-1. The KIR receptors, in the setting of HSCT, seem to be the most important NK cell receptor family. These receptors can either inhibit or activate NK cells with the difference between inhibitory and activating KIRs lying mainly in their intracytoplasmic tail. Inhibitory KIRs have long cytoplasmic tails (KIR-L) and activating KIRs have short cytoplasmic tails (KIR-S) with KIRs having two or three Ig-domains (KIR2D or KIR3D) [60-61].

In humans, the gene family encoding the *KIR* is located in the leukocyte receptor complex (LRC) on chromosome 19q13.4. To date, 15 genes have been well characterized, of which 9 are NK cell inhibitors (*KIR2DL1*, *KIR2DL2*, *KIR2DL3*, *KIR2DL4*, *KIR2DL5A*, *KIR2DL5B*, *KIR3DL1*, *KIR3DL2* and *KIR3DL3*), 6 are activating (*KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5* and *KIR3DS1*), and 2 are pseudogenes (*KIR2DP1* and *KIR3DP1*) [60-61]. An exception is *KIR2DL4* that although it has long tail it has an amino acid in the transmembrane region that allows an association with an accessory protein, FceRI-g, which confers an activating signal [62].

Individuals differ in the number and type of inherited *KIR* genes and the *KIR* haplotypes are divided into two groups, A and B. The A or AA haplotype has a fixed number of genes, all of which are inhibitory except for one activating gene (*KIR2DS4*). Haplotypes with addition-

al activating *KIR* genes (*KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, KIR3DS1)* or with *KIR2DL5* are either AB or BB and are grouped together as KIR Bx haplotypes. Often, the *KIR2DS4* gene is present in a deleted form and is not believed to be expressed at the cell surface. The "framework genes", *KIR3DL2, KIR3DP1, KIR2DL4,* and *KIR*3DL3, are common to both groups of haplotypes [60-61, 63].

The KIRs interact with some HLA class I antigens on target cells. HLA-Bw4 and distinct allotypes of HLA-C (C1 and C2 groups) are the main ligands for most KIRs [64]. HLA-C alleles are classified as C1 or C2 KIR ligand groups, depending on two amino acid positions encoded in exon 2. HLA-C1 allotypes have serine at position 77 and asparagine at position 80 and are ligands for the *KIR2DL2* and *KIR2DL3* inhibitory receptors. HLA-C2 allotypes have asparagine and lysine at positions 77 and 80, respectively and are ligands for the *KIR2DL1* inhibitory receptor and thought to be the ligand for the *KIR2DS1* activating receptor [65-66]. HLA-Bw4 allotypes are characterized by at least 5 different patterns of amino acids at positions 77 and 80-83 and are ligands for *KIR3DL1*. Some HLA-A alleles, namely 23:01, 24:02 and 32:01, are also ligands for *KIR3DL1* [67-71]. In addition, HLA-A3 and HLA-A11 are ligands for *KIR3DL2;* and HLA-A11 and some C1 and C2 allotypes are ligands for *KIR2DS4* [64, 72-74].The *KIR* gene and respective ligands are listed in Table 1.

KIR	FUNCTION	LIGAND
KIR2DL1	Inhibitory	HLA-C group 2
KIR2DL2	Inhibitory	HLA-C group 1
KIR2DL3	Inhibitory	HLA-C group 1
KIR2DL4	Inhibitory, activating	HLA-G
KIR2DL5	Inhibitory	Unknown
KIR3DL1	Inhibitory	HLA-B Bw4 and some HLA-A Bw4*
KIR3DL2	Inhibitory	HLA-A3 and HLA-A11
KIR2DS1	Activating	HLA-C group 2
KIR2DS2	Activating	Unknown
KIR2DS3	Activating	Unknown
KIR2DS4	Activating	HLA-A11 and subsets of HLA-C group 1 and group 2
KIR2DS5	Activating	Unknown
KIR3DS1	Activating	Unknown

* HLA-A*23:01, HLA-A*24:02 and HLA-A*32:01

Table 1. KIR receptors and their HLA ligands

The mechanism of recognition of a target cell by NK cells differs from others lymphocytes. [59] The NK cells are able to recognize a reduction or absence of self HLA class I ligands, as

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a form of distinguishing normal cells from target cells: this is the "missing-self recognition". It is well established that cancer cells and some infected cells develop various mechanisms to escape lysis by T cells [75-76]. An effective mechanism is to decrease or remove completely the HLA expression. The downregulation of HLA class I expression leads to resistance to lysis by T lymphocytes but, as a consequence, can lead to a susceptibility to lysis by NK cells [77-80]. During development, NK cells become licensed or educated by interaction with self-HLA molecules to maintain tolerance to normal tissues. NK cells that do not express inhibitory receptors for self are retained in an anergic or hypofunctional state and those which express inhibitory KIRs for self-HLA ligands are functionally active and thus can sense the lack of expression of self HLA molecules on target cells which triggers lysis of these cells. This is thought to be the main mode of action of NK cells [81-86].

Natural killer cell alloreactivity in hematopoietic stem cell transplantation

The clinical significance of missing-self recognition is especially evident in allogeneic HSCT. In HSCT the NK cell alloreactivity is determined by an analysis of the donor's *KIR* gene profile and by differences in MHC class I genes between the donor and the recipient. This can be better explained by the presence in the donor of NK cells expressing inhibitory KIRs that are not engaged by any of the HLA class I alleles present on the receptor [87]. As a consequence, donor NK cells become uninhibited and may display alloreactivity against mismatched allogeneic targets [81-86].

Furthermore, NK cells are relevant in the setting of HSCT because they are the first lymphoid cell subset to reconstitute after transplantation at a time when the adaptive immune system is impaired. They have been detected *in vivo* in recipients within 1 to 3 months after transplantation and up to 3 years after [88-91].

KIR model studies

Considering: 1) a strong correlation between the presence of *KIR* genes and their HLA ligands and cytotoxicity and 2) the advent of methods of precise genetic characterization, it is possible to determine the contributions of the various inhibitory and activating *KIR* genes in HSCT [92]. There are several models to define NK alloreactivity by *KIR* incompatibility or *KIR* mismatching, most of which are based on the analysis of *KIR* and HLA class I alleles. In the ligand-ligand model, the *KIR* expression is assumed following HLA typing. In this model, *KIR* ligands in recipients and donors are analyzed and at least one group of donor *KIR* ligands must to be absent in the recipient's *KIR* ligand repertoire. In the receptor-ligand model, the *KIR* genes are typed for the donor and the HLA alleles are analyzed for recipients and at least one of the inhibitory *KIR*s of the donor is not engaged in the recipient's ligand repertoire. Moreover some studies perform phenotypic analysis of inhibitory KIRs and CD94/NKG2A in donor NK cells and also functional assays which can provide more information about the degree of alloreactivity of NK cells [87,93-94]. It is difficult to know which model is the most adequate to select the *KIR* mismatch donor. Some authors suggest that an increasing number of receptor-ligand mismatch pairs increase the potency of the anti-leukemia effect and also suggest that the receptor-ligand model could improve the accuracy of the prediction of relapse rather than the ligand-ligand model in patients with lymphoid malig-

nancies [94]. However, it has not been well established and further studies are needed to confirm this hypothesis.

In addition, a novel observation emerged that NK cells of maternal donors of HSCT provided better protection from leukemia relapse than other related donors [95]. According to the authors, the better outcome of mother-to-child transplantation may be the result of the contact of maternal immune cells with the semi-allogeneic placenta during pregnancy. It was suggested that if further studies confirm the better outcomes of mother donors, it may be incorporated as a donor selection criterion.

Another interesting aspect was shown in a recent study with patients that received unrelated unmanipulated peripheral blood progenitor cells. The authors indicate that four-digit allele matching of HLA-C may have effects on the HSCT outcome dependent on the presence of C1 and C2 KIR epitopes in the patients [96] suggesting the importance of analysis of HLA-C at allele level for donor selection. While there are no common rules to select the best donor according *KIR* compatibilities, all the findings must be analyzed.

KIR genes and haploidentical hematopoietic stem cell transplantation

Full-haplotype mismatched (haploidentical) HSCT is an option to treat patients lacking a matched donor or a suitable UCB unit. In haploidentical HSCT (haplo-HSCT), the T cells present on allogeneic hematopoietic grafts are important to promote engraftment and mediate the GvL effect. However, they can also mediate GVHD [97-98]. These T-cell responses can be controlled by an appropriate intensity of immunosuppression by the conditioning regimen. The T-cell depletion of the graft help prevent GVHD but, as a consequence, T-cell depleted haplo-HSCT increases the risk of graft rejection and leukemic relapse. In this context, the presence of NK cell alloreactivity in the GVH direction seems to influence the prevention of leukemia relapse and has been investigated in several preclinical and clinical trials [89,99-100]. It has been observed that *KIR*-HLA mismatches can promote clinical benefits in haplo-HSCT especially in patients with acute myeloid leukemia (AML). In the first studies published by Ruggeri et al. [89,99] and the more recent updates in 2007 [100] appropriate KIR-Ligand incompatibilities were associated with a reduction in the risk of relapse of leukemia and graft rejection, and also protection against GVHD in patients with AML. These results were supported by animal models, in which the presence of NK alloreactivity was suggestive of a low incidence of acute GVHD due to the killing of host APCs, which are critical for inducing donor T-cell activation [101]. Similarly, experimental data suggest that the engraftment rate was improved as a result of the lysis of residual host T lymphocytes by alloreactive donor NK cells [89,99,101-102] and also that this contributed to the eradication of leukemia blasts that escaped from the conditioning regimen. These studies showed very good results and led to a novel concept of mismatch to search for a transplant donor. Since then, several investigations based on *KIR* mismatching have been carried out with different outcomes.

In a study of patients that received haplo-HSCT with T-cell depletion [94] *KIR* incompatibility (*KIR*-mismatch) was related to lower relapse rates in children with AML and also in children with acute lymphoid leukemia (ALL). Interesting, in the studies of Ruggeri et al.,

patients with ALL were not susceptible to *KIR*-ligand mismatched haplo-HSCT. The different result in these two groups may be related to the fact that Ruggeri et al. studied only adult patients. On the other hand, another recent study found no impact of *KIR* mismatch on children with chemoresistant ALL that received T-cell depleted Haplo-HSCT [103]. In general, NK cell alloreactivity seems to positively influence patients with myeloid malignancies and may benefit childhood ALL patients, but further studies are needed to confirm this.

A positive effect of NK cells on the outcome of haplo-HSCT in paedriatic patients was demonstrated in another study. The authors analyzed 21 children with different hematologic malignances and found anti-leukemia activity of alloreactive NK cells in most transplanted patients. They found that the NK cells derived from the donor were capable to selectively killing C1/C1 target cells, including the patient's leukemia blasts. Additionally, *KIR2DL2/3*+ NK cells that co-expressed *KIR2DS1* killed C2/C2 leukemic blasts. These data suggest that the presence of *KIR2DS1* in alloreactive NK cells may mediate potent cytotoxicity [91]. In agreement, in another study, the *KIR2DS1* expression in alloreactive NK cells conferred an advantage in the ability of NK cells to kill C2/C2 or C1/C2 myelomonocytic DCs and T-cell blasts [104]. Another recent study examined 86 patients with advanced hematologic malignancies who received nonmyeloablative, HLA-haploidentical HSCT with high-dose, post-transplantation cyclophosphamide. The inhibitory *KIR* gene mismatches between donor and recipient, or *KIR* haplotype AA transplant recipients of *KIR* genotype Bx donors, were associated with lower relapse and non-relapse mortality (NRM) and improved OS and event-free survival [105].

Nevertheless, other studies failed in find any association with *KIR* incompatibilities in the GVHD direction [106], or found worse outcomes of transplantation for donors with the potential to NK alloreactivity [107]. Using the ligand-ligand model in a study of 62 patients with ALL, AML and CML, the *KIR* mismatch was associated to considerably lower OS and a higher incidence of GVHD [107].

KIR genes and unrelated hematopoietic stem cell transplantation

The impact of KIR-ligand mismatching in HSCT using unrelated donors has been associated with controversial results. Beneficial outcomes have been shown in some studies. Unrelated HSCT KIR-ligand incompatibility was associated with a reduced incidence of grade III-IV acute GVHD and a better OS and disease free survival (DFS) in an analysis of 130 patients with different hematological malignances. The conditioning regimen included anti-thymocyte globulin (ATG) for T-cell depletion and the association with DFS remained significant even when patients with myeloid diseases were analyzed separately [108]. KIR-HLA incompatibilities were also associated with low rates of leukemic relapse in a study of 374 patients with myeloid malignances submitted to T-cell replete unrelated HSCT [109]. In this study, in spite of this beneficial result, the rates of graft failure were higher and there were no significant differences in DFS or transplant-related mortality. A large study described an advantage of donor NK alloreactivity; the authors analyzed 1770 patients of several centers and found that the absence of HLA-C2 or HLA-Bw4 ligands but not mismatches were associated with a decreased risk of relapse in recipients receiving unmanipulated grafts from unrelated donors [110].

Although most studies focus on the effect of the lack of inhibitory *KIR*s by their HLA class I pair, some studies have shown interesting results about the role of activating *KIR*s and *KIR* genotypes in unrelated HSCT. Certain B haplotype *KIR* groups have also been found to favorably affect the outcome after T-cell depleted HLA-identical sibling transplants [111]. In 2009 a study showed that donor group B haplotypes significantly improve graft survival in AML patients submitted to T-replete unrelated HSCT [112]. The same group in a recent report reconfirmed the influence of the B haplotype on transplantation outcome. They published a large study of 1409 unrelated transplants for AML and ALL and analyzed centromeric and telomeric gene-content motifs in both group A and B *KIR* haplotypes. They suggest that centromeric and telomeric motifs present in B haplotypes could promote protection against leukemic relapse, as well as, improve survival. Moreover, they found a reduced relapse in those patients whose donors had 2 or more B gene-content motifs [113]. In addition, in a prospective study, the presence of the B *KIR* genotype in donors was also related to fewer bacterial infections at six months post transplant in recipients of unrelated HSCT [114]. In fact it has been observed that some activating genes present in Haplotype B may have an influence on unrelated HSCT. The presence of *KIR3DS1* in the donor has been associated with reduced grade II-IV acute GVHD and a lower transplantation-related mortality rate [115-116]. Donor *KIR2DS1* in isolation or in association to *KIR2DS2* appears to provide protection against relapse in unrelated HSCT [116-117]. On the other hand, in an analysis of patients and their respective HLA-identical sibling or unrelated donors, *KIR2DS1* in the donor and the absence of this gene in the receptor was associated with increased risk of acute GVHD, *KIR2DS3* was associated to chronic GVHD and *KIR2DS5* was associated to relapse [118]. Another study also demonstrated deleterious effects of activating *KIR*s; an increased number of donor activating *KIR* genes was suggested to be a significant factor in the probability of relapse. The *KIR*-ligand mismatch pairs were a risk factor for transplant-related mortality [119]. The effect of activating *KIR*s was mainly found in AML and myelodysplastic syndrome (MDS) patients. The conditioning regimen included using ATG for *in vivo* T-cell depletion.

As discussed above, there are several studies describing improved outcomes based on *KIR*-ligand mismatching, however, most studies have reported no advantage [120-123] or worse outcomes for *KIR*-ligand mismatch donors in unrelated HSCT. Deleterious results included lower OS in patients with myeloid malignances submitted to *KIR*-ligand mismatch HSCT [120] increased infection rates [124]; increased probability of leukemic relapse [125] increased rates of rejection and association with acute Grade III and IV GVHD [126].

KIR genes and sibling hematopoietic stem cell transplantation

On applying *KIR* genotyping, some studies investigated the effect of *KIR* in sibling HSCT. A study of 220 donor-recipient pairs in HLA-matched sibling HSCTs found that patients with myeloid disease who were homozygous for the C2 group had worse OS than patients who were either homozygous or heterozygous for a C1 group. This effect was seen only in patients who received a graft from a donor carrying the *KIR2DS2* gene and only for patients with myeloid disease (no effect was seen in patients with lymphoid disease) [127]. In another study the *KIR*-ligand mismatch was associated to better DFS and OS and lower incidence of relapse in patients with AML and MDS that received T-cell depleted HLA-identical sibling transplants.

AML and MDS patients who lacked two HLA ligands for donor-inhibitory *KIR* had the highest DFS and OS. Interesting, these results were found only for AML and MDS patients and not for CML or ALL patients [128]. Benefits were also described for AML and MDS patients in another study; the authors found a reduced risk for relapse in patients undergoing HLA-identical sibling HSCT who both received a high (above-median) NK cell number and lacked at least one HLA-B or HLA-C ligand of the donor's inhibitory *KIR*s. Transplants with more than two different activating donor *KIR*s were associated with an increased risk for non-relapse mortality [129]. In another study, *KIR*-genotyping of 246 T-cell depleted HSCTs with HLA-identical sibling donors was performed; the *2DL5A*, *2DS1*, and *3DS1 KIR* genes were associated with significantly less relapse in patients with AML but not in patients with other myelogenous or lymphoid malignancies. All these findings suggest that NK cells have implications in donor selection for myeloid diseases especially for AML patients [130].

Some studies have investigated *KIR* genes in respect to post-transplant infections in sibling HSCT. In one study, additional activating *KIR* genes in the donor compared to the recipient's genotype were associated with lower transplant related mortality, better survival, and a reduced incidence of cytomegalovirus (CMV) reactivation [131]. In another study of T-cell replete HSCT from matched sibling donors, the presence of donor *KIR* haplotype B was associated with a 65% reduction in CMV reactivation [132]. Moreover, in another the presence of specific activating *KIR* haplotypes in the donor was associated with protection from CMV reactivation in patients submitted to sibling and unrelated HSCT [133]. Other researchers analyzed patients according to the combination of group A and B *KIR* haplotypes in the transplant donor and recipient and found a higher OS when the donor lacked and the recipient had group B *KIR* haplotypes. Moreover, the poorest OS rate and increased relapse and acute GVHD were recorded when the donor had and the recipient lacked group B *KIR* haplotypes and both were homozygous for the C1 *KIR* ligand. The presence of the Bw4 ligand was also associated with increased acute GVHD. In contrast, the presence of both *KIR3DL1* and its cognate Bw4 ligand was associated with decreased non-relapse mortality. An analysis of *KIR* genes individually revealed *KIR2DS3* as a protective factor for chronic GVHD [134]. In another study, 60 AML patients submitted to T-cell replete HLA-matched related donor allogeneic bone marrow transplants were analyzed. Heterozygous C1/C2 patients had significantly worse survival than those homozygous for C1 or C2 and the C1/C2 group had a higher relapse rate. Multivariate analysis found C1/C2 status to be an independent predictor for mortality. Since C1/C2 heterozygotes have a greater opportunity to engage inhibitory *KIR*s than C1 or C2 homozygotes, they may more effectively inhibit *KIR*-positive NK cell and T cell populations involved in GvL responses [135].

KIR genes and autologous stem cell transplantation

Few research groups have demonstrated the influence of *KIR* genes in autologous stem cell transplantation (ASCT). The interest in the role of *KIR* genes in the setting of ASCT is mainly related to preventing relapse, the main cause of treatment failure. Some studies have shown that rapid and early NK cell recovery following ASCT is associated with a better progression-free survival (PFS) in some diseases. An analysis of 182 patients with myeloma multiple submitted to ASCT showed a worse outcome in patients who were *KIR3DS1*+. The

KIR3DS1 genotype was associated with a shorter PFS with the effect being more notable in patients who received a transplant while in complete or partial remission after induction chemotherapy and those who lacked HLA-Bw4 [136].

Similarly, in a study of 169 neuroblastoma patients treated by ASCT, a survival advantage was shown in patients lacking HLA class I ligands for autologous inhibitory KIRs. Those who lacked the HLA-C1 ligand for *KIR2DL2*/ *KIR2DL3* had the highest 3-year survival rate [137]. Another study analyzed the influence of KIR mismatch in ASCT by the receptor-ligand mismatch model. The study, involving 16 patients who were submitted to ASCT for non-Hodgkin's lymphoma and solid tumours, found a reduced relapse rate for patients with an inhibitory KIR-HLA mismatch [138]. On the other hand, another study of 67 patients with solid tumors or lymphomas who were treated with ASCT did not find any effect of KIR-ligand interactions on the outcomes of ASCT [139].

KIR genes and unrelated umbilical cord blood transplantation

Unrelated UCBT has proved to be a viable treatment option. An advantage of using UCB is the relatively low risk of acute GVHD due to a lower number of mature donor T cells and thus an increased possibility of using HLA-mismatched units. Moreover, UCBT, as in haplo-HSCT, is characterized by a rapid post-transplant recovery of NK cells. An analysis of 218 patients with AML or ALL showed that patients who received a single UCBT unit from a *KIR* ligand incompatible donor showed a lower incidence of relapse, and increased DFS and OS [140]. Additionally, as was seen in the Ruggery studies, the benefits were significantly more marked in patients with AML. However, another study failed to observe any benefit of KIR-ligand mismatch in 155 recipients of UCB after myeloablative conditioning. In fact, in 102 patients who received UCB after nonmyeloablative conditioning, *KIR*-Ligand mismatch was associated with an increased rate of acute GVHD and higher treatment-related mortality [141].

Altogether these data show that simple assessments of the *KIR* genotype might help in the selection of donors for HSCT. *KIR* mismatches seem to be effective in haplo-HSCT and mainly in patients with myeloid diseases. The contradictory results reported about the influence of *KIR* mismatches in the diverse types of HSCT can certainly be explained by differences in the transplant protocols employed. Differences like number of patients analyzed, type of disease studied, stage of the disease, patient age, conditioning regimen, stem cell source, GVHD prophylaxis and variability in the definition of *KIR* mismatch can influence transplant outcomes. Factors like T-cell depletion and no post-transplant immune suppression seem to be important in maximizing NK cell alloreactivity [142].

Cytokines genes and receptors in HSCT

There are many other genetic factors that influence to outcome of transplant, independent of whether the transplant is autologous, allogeneic, matched or mismatched, sibling or unrelated donor, or haploidentical and of whether the cell source is bone marrow, peripheral blood or UCB.

The goal of the majority to studies is to know what kind of influence these genetic factors and HLA compatibility have and what effect they have on the course of the transplant: acute and chronic GVHD, relapse, OS and mortality.

One important factor is the polymorphisms within the regulatory sequences of cytokine genes. Proinflammatory cytokines, receptors and related inhibitors have been implicated in a large number of immune diseases. The main role of cytokine genes is related to the immunopathogenesis of GVHD [143].

Studies on cytokine genes in the transplant setting involve receptors of the TNF, IL-10, the IL-1 gene family, IL-2, IL-6, interferon TNF-γ, TGF-β1 and TGF-β1 [28, 144-145].

Tissue injury, including of the mucosa and liver, occurs during the conditioning regimen. This process causes the secretion of the TNF-α, IL-6 and IL-1 pro-inflammatory cytokines that increase HLA antigens, thus increasing the antigens recognized by donor T-cell receptors in allogeneic transplantation. Moreover, during the activation to donor cells, T cells produce IL-2 and INF-γ (Th1) that trigger GVHD and are balanced for Th2 cytokines such as IL-4 and IL-10 [146-147].

Studies on allogeneic HSCT, investigated 16 patients with chronic GVHD by a systematic clinical examination of the oral cavity, and by biopsies of the buccal mucosa and labial salivary glands. The findings demonstrated that the mRNA expression of IL-2, INF-γ, IL-4 and IL-5 in the buccal mucosa of chronic GVHD patients was greater than in control individuals. A similar result was detected for the labial salivary glands with the addition of IL-10 [148].

Studies show that IL-2 and INF-γ were detected more frequently in patients with acute GVHD. Additionally, IL-12 and IL-18 were increased while IL-10 was decreased in the same group, and IL-4 did not present a significant difference between the control and patient groups [144]. Other studies show high IL-10 gene expression in the recipient that may be related to a reduced incidence of grades II to IV acute GVHD and a reduced graft-versus-tumor effect after HSCT with nonmyeloablative conditioning [145].

On the other hand, studies affirm that IL-4 producing cells inhibit the development of acute GVHD and the increased percentage of IL-4 secreting cells may be responsible for the unexpected low incidence of acute GVHD after peripheral blood HSCT, despite the presence of large numbers of mature T cells in the donor infusion [148].

Many studies show that polymorphisms of cytokine genes influence to outcome of transplants, such as with the development of GVHD. One example is that the *IL17+197*^{a} allele was associated with increased risk of grade III and IV acute and chronic GVHD. Other studies demonstrate clinically important relationships between genetic polymorphisms in TNF-α and the severity of acute GVHD [147,149]. There are many other associations of polymorphisms of cytokine genes that course to acute and chronic GVHD.

Major histocompatibility complex class I-related chain genes and HSCT

The MHC class I-related chain (*MIC*) genes have been the subject of interest in the setting of HSCT. This family of genes, located in the MHC classical class I region, was first described in 1994 [150-151]. These genes are very polymorphic, but not as much as the classical HLA class I genes. Humans have seven *MIC* genes, named *MICA* to *MICG* but only two *MIC* genes are functional, the MHC class I-related chain A (*MICA*) and B (*MICB*) genes. The MIC proteins are similar to the HLA class I gene products however they are not associated with

β-2-microglobulin and also do not bind peptides to present to T cells [150,152]. MIC proteins appear to be induced by stress [153] and are expressed on the cell surface of fibroblasts and endothelium cells [154]. They are ligands for NKG2D [155], a receptor present on NK cells and some T cells, and because of this they can co-stimulate NK cells and T cells and can therefore determine the outcome of certain effector functions that are related to GVHD. In fact, *MIC* genes have been show to be attractive targets in diverse cancers, autoimmune diseases and in organ rejection after transplantation.

Several studies have demonstrated that the MICA may be a target molecule in allograft rejection because MICA can elicit antibody production after solid organ transplantation [156-163]. Some studies have reported diverse outcomes in HSCT related to *MIC* genes. It was suggested that *MIC* genes play a role in GVHD in HLA-matched HSCT because a higher rate of grade II-IV acute GVHD was found as was more gastrointestinal GVHD in MICA mismatched patients [164]. In addition, matches of MICA and MICB loci were shown to increase patient survival in a study of 44 patients who received unrelated HSCT [165].

Some polymorphisms in *MICA* genes have also been associated to outcomes in transplants. A change at position 129 of the α2-heavy chain domain of *MICA* can denote the strength of interaction with the NKG2D receptor. The presence of methionine at position 129 of the *MICA* gene characterizes a strong binder, and the presence of valine characterizes a weak binder [166]. Hence, the *MICA*-129 valine genotype and soluble *MICA* serum level were considered risk factors for chronic GVHD in a study of 211 HLA-identical sibling pairs of HSCT while before transplantation, the presence of anti-*MICA* antibodies that can neutralize soluble *MICA* confers protection [167]. Altogether, these data suggest that *MIC* genes, in particular the *MICA* genes, could be used as biomarkers for chronic GVHD and should be studied further.

Minor histocompatibility antigens and HSCT

The human minor histocompatibility antigens (mHAgs) are another group of immunogenic peptides, distinct from the MHC system, which seem to have a role in HSCT outcomes. They are derived from intracellular polymorphic proteins and are presented by HLA class I and II restricted T cells [168-170]. Accumulated evidence suggests that they can elicit allogeneic T-cell mediated immune response in HLA-matched allogeneic HSCT and because of this have been investigated in order to understand their possible role in the control of GVHD and GvL.

Diverse minor histocompatibility antigens of various genetic and cellular origins have been described. More than 40 different genes that encode mHAgs recognized by either CD8+ or CD4+ T cells have been identified [171-174]. Most of the mHAgs are result of non-synonymous single nucleotide polymorphisms in autosomal genes while others are encoded by the sex chromosomes. At least 6 genes in the Y chromosome encode male-specific MHAgs (so-called HY antigens). Additionally, mHAgs may also be caused by gene deletions and genetic variations in non-coding regions affecting gene transcription [175-178].

The best-characterized minor histocompatibility antigen is encoded by the Y chromosome (HA-1). The mHAgs related to gender seems to be involved in HSCT outcomes because their

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absence in women can lead to a response to male antigens; female-to-male transplants seem to be more susceptible to GVHD [168-170, 179-180,181-185]. Antibody responses to HY proteins are also associated with both chronic GVHD and the maintenance of remission [186], but whether these antibody responses contribute meaningfully to GVHD, or simply serve as markers for it, remains unclear. In spite of female-to-male immune responses being more common, the opposite can also happen [187-188].

Some mHAgs are expressed only in the hematopoietic system while others are also expressed in normal tissues. mHAgs whose expression is limited to hematopoietic tissue may be recognized by specific donor T cells and may selectively contribute to a GvL effect and those with broad tissue expression may mediate GVHD [189].

Several studies have associated the presence of mHAg-specific T cells post-transplantation with graft rejection [179, 190], GVHD [191-194], and the GVL effect [195-197]. Mismatches between patient and donor for HA-1, HA-2, HA-4 and HA-5 are associated with an increased incidence in GVHD [191].

The role and the mechanisms of alloreactions related to mHAgs are not fully understood, but these data suggest that they may be relevant in determining post-transplantation outcomes.

4. Conclusion

Genetic differences between donor and recipient are crucial factors capable of influencing transplantation outcomes. Much has been learned about the HLA and non-HLA genes, their expression, their polymorphisms and their role in mediating GvL and GVHD responses. A better understanding of these genes may permit more refined donor selection criteria and consequently a more accurate assessment of transplant-related complications.

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