Histocompatibility

9

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9.1 Introduction

Immune-mediated rejection of tissue allografts was first described in 1945 by the British immunologist Peter Medawar, followed by the discovery of the major histocompatibility complex (MHC) carrying the histocompatibility genes by Peter Gorer and George Snell in 1948, and of the human leukocyte antigen (HLA) molecules by Jean Dausset, Jon van Rood, and Rose Payne a decade later (Thorsby 2009). The importance of these discoveries was recognized by the Nobel Prices in Physiology and Medicine to Medawar, Snell, and Dausset in 1960 and 1980, respectively. Since then, the MHC has emerged as the single most polymorphic gene locus in eukaryotes, with 17,695 HLA alleles reported to date in the IMGT/HLA database, Release 3.31.0, 2018/01/19 (Robinson et al. 2015). While the main barrier to successful tissue grafting remain the HLA incompatibilities, also non-HLA polymorphisms have been recognized as important players, in particular minor histocompatibility antigens (mHAg), killer immunoglobulin-like receptors (KIR), and other polymorphic gene systems (Dickinson and Holler 2008; Gam et al. 2017; Heidenreich and Kröger 2017; Spierings 2014).

9.2 The Biology of Histocompatibility

9.2.1 Major Histocompatibility Antigens

The human MHC is located within ~4 Mbp of DNA on the short arm of chromosome 6 (6p21.3) and contains ~260 genes, many of which with immune-related functions (Trowsdale and Knight 2013). The MHC falls into three main regions, class I, II, and III, containing HLA A, B, and C; HLA DR, DQ, and DP; and complement factor as well as tumor necrosis factor genes, respectively. MHC genes are codominantly expressed and inherited following Mendelian rules, with a resulting 25% probability for two siblings to be genotypically HLA identical, i.e., to have inherited the same MHC from both parents. An additional hallmark of the MHC is linkage disequilibrium (LD), i.e., the nonrandom association of alleles at different HLA loci, and relatively high recombination rates of over 1%, also referred to as "crossing over" (Martin et al. 1995).

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E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_9

9.2.2 HLA Class I and II Structure and Function

The classical HLA class I and II molecules are cell surface immunoglobulins (Ig) presenting peptides in their highly polymorphic antigen-binding groove (Madden 1995). HLA class I A, B, and C molecules are heterodimers of a polymorphic α chain of higher molecular weight (MW) than the monomorphic β2 microglobulin (heavy and light chain of 45 kDa and 12 kDa, respectively). The α-chain contains three hypervariable Ig-like domains, two of which form the antigen-binding groove while the third is involved in contacting the CD8 coreceptor on T cells, and the transmembrane region. HLA class I molecules are expressed on all healthy nucleated cells. They present peptides, i.e., protein fragments of mostly intracellular origin generated by proteasomal cleavage and transported to the endoplasmic reticulum via the transporter associated with antigen processing (TAP) (Vyas et al. 2008). Cell surface HLA class I peptide complexes can be recognized by the T cell receptor (TCR) of CD8+ T cells, leading to the activation of cytotoxic and/or cytokine effector functions, or by KIR on natural killer (NK) cells, leading to the inhibition of effector functions. HLA class II DR, DQ, and DP molecules are heterodimers of an α- and a β-chain of similar MW of approximately 30 KDa each, both with a transmembrane part anchored to the cell membrane. Most of the polymorphism is clustered in the β-chain Ig-like domain forming the antigen-binding groove, whose overall structure is similar to that of HLA class I, and the region contacting the CD4 coreceptor on T cells is also located in the β-chain. HLA class II proteins are expressed on professional antigen-presenting cells, as, for example, B cells, macrophages, and dendritic cells. Moreover, HLA class II protein expression on various cell types can be upregulated by proinflammatory cytokines such as IFNγ and TNFα. HLA class II presents peptides generally of extracellular origin generated through degradation of proteins in the phagolysosome (Vyas et al. 2008). Peptide loading onto HLA class II molecules takes place in the dedicated MIIC compartment and is catalyzed by two nonclassical HLA molecules equally encoded in the MHC, HLA DM, and DO. After transport to the cell surface, HLA class II peptide complexes can be recognized by the TCR of CD4+ T cells, leading to the activation of cytokine-mediated helper or regulatory functions. HLA class II receptors on NK cells, analogous to KIR for HLA class I, have not been described to date.

9.2.3 HLA Polymorphism and Tissue Typing

HLA molecules were first detected by serological methods, through the ability of sera from sensitized individuals to agglutinate some but not all leukocytes (hence the term “human leukocyte antigen”) (Thorsby 2009). Until the mid-1990s, serological typing was the main method for tissue typing. With the advent of polymerase chain reaction (PCR) techniques, molecular tissue typing took over and unraveled a far greater degree of HLA allelic polymorphism than previously appreciated (Erlich 2012). HLA nucleotide polymorphism is clustered in so-called hypervariable regions (HvR) mainly in exons 2, 3, and 4 of HLA class I and exons 2 and 3 of HLA class II, encoding the functional antigen-binding groove and CD4/CD8 coreceptor-binding regions. Therefore, PCR-based molecular typing focused on these exons, leading to different levels of typing resolution (Table 9.1). With the advent of next-generation sequencing (NGS) for tissue typing purposes (Gabriel et al. 2014), allelic or at least high-resolution typing can be achieved in most cases. Moreover, NGS enables high-throughput sequencing of the entire HLA coding and noncoding regions, unraveling an additional layer of polymorphism with hundreds of new alleles reported to the IMGT/HLA database every month.

9.2.4 T Cell Alloreactivity

The ability of T cells to specifically recognize non-self, allogeneic tissues is called T cell

Table 9.1 HLA typing resolution and appropriate typing methods

HLA typing resolution[a]	Appropriate typing methods[b]
Low (first field)	Serology, SSP, SSOP, others
High (second field)	NGS, SBT
Allelic (all fields)	NGS, SBT
Intermediate	SSP, SSOP, SBT

[a]As defined in (Nunes et al. 2011). *Low:* A serological typing result or DNA-based typing at the first field in the DNA-based nomenclature. *High:* A set of alleles that encode the same protein sequence in the antigen binding site and that exclude alleles not expressed at the cell surface. High resolution thus includes alleles reported with the suffix G (set of alleles with identical nucleotide sequence across the exons encoding the antigen binding site) or the suffix P (set of alleles encoding the same protein sequence at the antigen binding site). *Allelic:* Unique nucleotide sequence for a gene as defined by the use of all of the digits in a current allele name. Intermediate: A level of resolution that falls between high and low resolution, as agreed with the entity requesting the testing. Examples are restriction to common and well-documented (CWD) alleles (Sanchez-Mazas et al. 2017) or reporting by NMDP codes (https://bioinformatics.bethematchclinical.org/hla-resources/allele-codes/allele-code-lists/).

[b]*Serology* complement-dependent cytotoxicity of specific antisera, *SSP* sequence-specific priming, *SSOP* sequence-specific oligonucleotide probing, *Others* additional molecular typing approaches including quantitative PCR and restriction fragment length polymorphism (RFLP), *SBT* sequencing-based typing (Sanger sequencing), *NGS* next-generation sequencing

alloreactivity. It can be either direct or indirect. Direct T cell alloreactivity is targeted to intact mismatched HLA peptide complexes expressed on the cell surface of allogeneic cells and can be mediated by both naïve and memory T cells (Archbold et al. 2008). Indirect T cell alloreactivity refers to the recognition of peptides derived by proteasomal cleavage from mismatched HLA and presented in the antigen-binding groove of self HLA molecules (Gokmen et al. 2008). These peptides are also referred to as Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE, see Sect. 9.3.3) (Geneugelijk and Spierings 2018). A special form of indirect T cell alloreactivity is the recognition of foreign peptides not deriving from mismatched HLA but from any other expressed polymorphic gene and presented by self HLA molecules. These peptides are referred to as minor histocompatibility antigens (mHAg) (Spierings 2014). mHAg are the only targets of T cell alloreactivity in HLA-matched hematopoietic cell transplantation (HSCT) and are mainly recognized by naïve T cells. T cell alloreactivity is the main mediator of both the major benefit and the major toxicity of allogeneic HSCT, represented by immune control of residual malignant disease (graft versus leukemia; GvL) and immune attack of healthy tissues (graft versus host disease; GvHD), respectively.

Key Points

- HLA molecules are encoded by highly polymorphic genes in the human MHC and play a crucial role for peptide antigen recognition by T cells.
- HLA tissue typing can be performed at different levels of resolution, the highest being attainable only by NGS-based methods, which are unraveling an unprecedented degree of polymorphism in the MHC.
- Alloreactive T cells can recognize non-self HLA molecules on healthy and malignant cells after Allo-HSCT, mediating both toxic GvHD and beneficial GvL.

9.3 HLA Matching in Allogeneic HSCT

9.3.1 Donor Types

In HLA identical sibling HSCT, patient and donor have inherited the same parental MHCs, an event occurring with a likelihood of 25% according to Mendelian rules. Genotypic HLA identity should be confirmed by family studies for all six HLA loci (to exclude recombination). Haploidentical donors share only one MHC haplotype while the other haplotype is different. These donors are available for more than 90% of patients and can be found in parents or offsprings (100% likelihood), siblings (50% likelihood), as well as the extended family. Also HLA

haploidentity should be confirmed by family studies wherever possible. Unrelated donors (UD) can be found among over 30 million volunteers enrolled in the worldwide registries or from over 700,000 banked cord blood units. The probability to find a volunteer UD matched for 8/8 HLA A, B, C, and DRB1 alleles varies according to the ethnic group of the patient between 30% and over 90% (Gragert et al. 2014). For UD HSCT, HLA identity should be confirmed at the highest resolution level possible (allelic, high, or intermediate resolution, Table 9.1), to be agreed between the transplant center and the tissue typing laboratory.

9.3.2 Clinical Impact of HLA Mismatches

The clinical relevance of histocompatibility for the outcome of HSCT is significantly influenced by different patient-, donor-, and transplant-related factors (Table 9.2). The most striking example for the impact of these confounding factors is the advent of haploidentical HSCT, in which successful transplantation across an entire mismatched haplotype was rendered possible by extensive T cell depletion of the graft and, more recently, by innovative schemes of pharmacological GvHD prophylaxis (Slade et al. 2017). On the other hand, haploidentical HSCT has been associated with a particular form of immune escape relapse characterized by the selective genomic loss of the mismatched HLA haplotype, with important implications for treatment strategies (Vago et al. 2012). In UD HSCT, high-resolution matching for 8/8 HLA A, B, C, and DRB1 alleles has been shown to be associated with the best clinical outcomes, with an approximately 10% decrease in survival probabilities for every (antigenic or allelic) HLA mismatch at these four loci (Lee et al. 2007). On the other hand, the impact of HLA disparity was shown to be significantly reduced by advanced disease status at transplant, again demonstrating the inextricable link between HLA mismatches and confounding factors. The notion that there will be no "one-size-fits-all" solution to the question on the impact of histocompatibility in HSCT has to be taken into account when critically interpreting studies in this complex field.

Table 9.2 Confounding factors of HLA/non-HLA immunogenetics and HSCT outcome

Confounding factor[a]	
Patient related	Age, sex, ABO, CMV serostatus, diagnosis, disease status
Donor related	Age, sex, ABO, CMV serostatus
Transplant related	Conditioning, GvHD prophylaxis, stem cell source, and composition

[a]The impact of HLA matching is additionally confounded by non-HLA immunogenetic factors and vice versa

9.3.3 Models of High-Risk/Nonpermissive HLA Mismatches

HLA mismatches that are clinically less well tolerated than others are referred to as high risk or nonpermissive. This is based on the observation that limited T cell alloreactivity is generally sufficient for the beneficial effect of GvL without inducing clinically uncontrollable GvHD, while intolerable toxicity can be induced by excessive T cell alloreactivity leading to severe treatment refractory GvHD. Therefore, high-risk or nonpermissive HLA mismatches are those associated with excessive T cell alloreactivity compared to their low-risk or permissive counterparts. Different models have been developed over the past years for their identification (Table 9.3). They rely on the presence of shared or nonshared T cell epitope (TCE) groups between mismatched HLA DPB1 alleles (Fleischhauer and Shaw 2017), genetically controlled expression levels of mismatched HLA C or DPB1 alleles in the patient (Petersdorf et al. 2014, 2015), specific high-risk HLA C and DPB1 allele mismatch combinations identified by retrospective statistical association between mismatch status and clinical outcome (Fernandez-Vina et al. 2014; Kawase et al. 2009), and the total number of PIRCHEI (presented by HLA class I) and PIRCHEII (presented by HLA class II) as a measure of the potential level of indirect alloreactivity after transplantation (Geneugelijk and

Table 9.3 Models of high-risk/nonpermissive HLA mismatches

Model	HLA locus, donor type, and clinical association
T cell epitope (TCE) groups[a]	HLA-DPB1; 8/8 UD; mortality and acute GvHD
Expression levels[b]	HLA C and DPB1; 7–8/8 UD; acute GvHD
Mismatch combinations[c]	HLA C and DPB1; 7–8/8 UD; mortality, acute GvHD and relapse
PIRCHE[d]	HLA C and DPB1; 8/8 UD; acute GvHD

[a]*TCE groups:* HLA DPB1 mismatches involving alleles from the same (permissive) or different (nonpermissive) TCE groups (Fleischhauer and Shaw 2017)
[b]*Expression levels:* HLA C or DPB1 mismatches involving a high-expression allele in the patient, as predicted by noncoding single nucleotide expression polymorphisms (Petersdorf et al. 2014, 2015)
[c]*Mismatch combinations*, high-risk allele mismatches defined by statistical associations (Fernandez-Vina et al. 2014; Kawase et al. 2009)
[d]*PIRCHE*, predicted indirectly recognizable HLA epitope numbers as predicted by online tools (Geneugelijk and Spierings 2018)

Spierings 2018). It should be noted that HLA DPB1 mismatches are present in over 80% of 8/8 matched UD HSCT, and models for high-risk or nonpermissive mismatches at this locus are therefore of particular practical relevance. The PIRCHE model is attractive since it is potentially applicable to any HLA-mismatched donor transplantation including <8/8 matched UD and haploidentical HSCT; on the other hand, clinical evidence for its validity in HSCT has so far been obtained only on relatively limited transplant cohorts. As stated above (Sect. 9.3.2), it is crucial that any of these or future models be tested in independent cohorts of sufficient statistical size and that they be continuously revalidated as clinical transplant practice and hence potential confounding factors evolve.

9.3.4 Guidelines for UD Selection by Histocompatibility

Consensus guidelines for donor selection have been established in many countries both in Europe and overseas, through the collaboration between donor registries and national immunogenetic societies. The general recommendation is the selection of an 8/8 HLA A, B, C, and DR (in Europe often 10/10, i.e., including the HLA DQ locus) matched UD if an HLA identical sibling is not available, followed by a 7/8 (or 9/10) UD or a haploidentical donor. Avoidance of high-risk or nonpermissive HLA mismatches according to any of the models outlined in Table 9.3 is usually regarded as optional, with particular emphasis on the avoidance of nonpermissive HLA DPB1 TCE mismatches since the TCE model is the only one to have been validated in different independent clinical studies to date (Fleischhauer and Shaw 2017). Also the inclusion of some of the non-HLA immunogenetic factors outlined in Sect. 9.4 can be considered, in particular with regard to donor KIR typing in haploidentical HSCT (Heidenreich and Kröger 2017).

Key Points

- HSCT donor types (in parenthesis the % probability of their identification for a given patient) include genotypically HLA identical siblings (25%), HLA haploidentical family donors (>90%), UD (30–90%), and cord blood donors (>80%).
- HLA typing strategies including family studies for related donors and typing resolution level for UD should be agreed between the transplant center and the tissue typing laboratory.
- The clinical relevance of HLA matching for the outcome of HSCT is critically dependent on numerous patient-, donor-, and transplant-related factors.
- In UD HSCT, survival probability decreases by 10% with every mismatch at HLA A, B, C, and DRB1, in patients transplanted at early disease stage.
- Models for high-risk nonpermissive HLA mismatches eliciting excessive T cell alloreactivity with intolerable toxicity include structural TCE, expression levels, specific allele

combinations, and PIRCHE. All these and future models need to be tested in independent cohorts of sufficient statistical size and be continuously revalidated as clinical transplant practice evolves.
- Consensus guidelines established at the national level between donor registries and immunogenetic societies aid in the selection of HSCT donors.

9.4 Non-HLA Immunogenetic Factors

9.4.1 Overview

HLA alleles are the most but not the only polymorphic genes in humans. Overall, interindividual gene variability by single nucleotide polymorphism (SNP) or copy-number variation (CNV) affects 0.5% of the 3×10^9 bp in the human genome. Although most of these polymorphisms are probably nonfunctional, some of them can give rise to polymorphic proteins that can be mHAg as described in Sect. 9.2.2, affect the expression of different genes including those encoding immunologically active cytokines, or act themselves as immune ligands or receptors relevant to transplantation biology. Among the latter, the KIR gene locus on the long arm of human chromosome 19 displays considerable polymorphism, with 907 alleles reported to the IPD/KIR database, Release 2.7.0, July 2017 (Robinson et al. 2005). Similar to high-risk or nonpermissive HLA mismatches, the role of non-HLA polymorphism in allo-HSCT is still incompletely defined. It is impossible to give a comprehensive overview of all non-HLA factors under study, and the list of factors listed in Table 9.4 and discussed in Sect. 9.4.2 is only a selection based on existing evidence for their clinical impact in certain transplant settings.

Table 9.4 Non-HLA immunogenetic factors and HSCT outcome

Non-HLA factor	Clinical outcome association
mHAg[a]	GvHD and relapse
KIR[b]	Relapse and mortality
MIC[c]	GvHD, relapse, and transplant-related mortality
Others[d]	GvHD and transplant-related mortality

[a]*Minor histocompatibility antigens* (Spierings 2014)
[b]*Killer Ig-like receptors* (Heidenreich and Kröger 2017; Shaffer and Hsu 2016)
[c]*MHC class I-related chain* (Isernhagen et al. 2016)
[d]*Cytokine, chemokine, and immune response gene polymorphisms* including tumor necrosis factor, interleukin (IL)10, the IL1 gene family, IL2, IL6, interferon γ, tumor growth factor β and their receptors, NOD-like receptors (NOD2/CARD15), toll-like receptors, micro-RNAs (Dickinson and Holler 2008; Gam et al. 2017; Chen and Zeiser 2018)

9.4.2 Clinical Impact of Non-HLA Immunogenetic Factors

mHAg are the only targets of T cell alloreactivity in HLA identical HSCT (see Sect. 9.2.2) and as such play an important role for both GvHD and GvL (Spierings 2014). This dual function is related to their different modes of tissue and cell expression, i.e., hematopoietic system restricted or broad. Broadly expressed mHAg can cause both GvHD and GvL, and donor-recipient matching for these mHAg is therefore desirable yet virtually impossible due to their large number, with many of them probably currently undefined. In contrast, mHAg restricted to hematopoietic cells are more prone to induce selective GvL. The latter are being explored as targets for HSCT-based immunotherapy of hematological malignancies, in which mHAg-specific responses are specifically enhanced to promote GvL.

KIR are predominantly expressed by NK cells and recognize certain HLA class I specificities on target cells. KIR have either long inhibitory or short activating cytoplasmic domains and are stochastically coexpressed on NK cells. The eventual outcome of KIR interaction (or lack thereof) with its HLA class I ligand (inhibition or activation) is a complex process that depends on the relative number of inhibitory or activatory KIR

and on the state of education of the NK cell. Educated NK cells from individuals expressing the cognate HLA ligand are strongly reactive against cells missing that ligand. This "missing self" reactivity is at the basis for the potent GvL effect attributed to NK cells in the setting of HLA-mismatched transplantation, in particular haploidentical HSCT (Heidenreich and Kröger 2017). Depending on the donor KIR gene asset, a role for NK cell-mediated GvL has also been postulated in the HLA-matched setting (Shaffer and Hsu 2016). Based on all this evidence, KIR typing is increasingly being adopted as an additional criterion for donor selection.

MHC class I chain-related (MIC) A and B are nonclassical MHC class I genes. MICA encodes a ligand for NKG2D, an activating NK receptor. The SNP Val/Met at position 129 of the MICA protein results in isoforms with high (Met) and low affinities (Val) for NKG2D. Consequently, various studies suggest a role for this SNP in SCT outcome, including GvHD, relapse and survival (Isernhagen et al. 2016).

Immune response gene polymorphisms have also been reported to contribute to the risks associated with HSCT (Dickinson and Holler 2008; Gam et al. 2017; Chen and Zeiser 2018). They often comprise SNPs in cytokine or chemokine-coding genes or their regulatory elements such as micro-RNAs (miRNAs). These variations in both the donor and the recipient can have a significant impact on transplant outcome and the development of GvHD; however, their relative role in different transplant settings is not yet fully elucidated.

Key Points

- Non-HLA immunogenetic factors that have been associated with clinical outcome of HSCT include polymorphic mHAg, KIR, MIC, and immune response genes.
- Hematopoietic tissue-specific mHAg are being exploited for specific cellular immunotherapy of hematologic malignancies.
- Polymorphic KIR are responsible for "missing self" recognition by alloreactive NK cells mediating selective GvL after HSCT, and KIR genotyping is therefore increasingly included into donor selection algorithms.

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