

HLAMatchmaker-based definition of structural human leukocyte antigen epitopes detected by alloantibodies

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Purpose of review

This review addresses the concept that human leukocyte antigen (HLA) antibody specificity should be determined to HLA epitopes rather than HLA antigens.

Recent findings

HLAMatchmaker is a computer algorithm that considers small configurations of polymorphic residues referred to as eplets as essential components of HLA epitopes. This overview describes recent developments that have increased our understanding of structural epitope antigenicity, that is, reactivity with specific antibody and immunogenicity, that is, its ability to induce an antibody response.

Summary

A determination of the repertoire of immunogenic epitopes is important for HLA compatibility testing and the identification of acceptable mismatches for sensitized patients.

Keywords

antigenicity, HLAMatchmaker, human leukocyte antigen antibody, human leukocyte antigen epitope, immunogenicity

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Introduction

It is now well recognized that human leukocyte antigen (HLA) class I and class II antibodies represent significant risk factors for transplant failure. Such antibodies are the result of immune responses to mismatched HLA antigens, which can occur before transplantation following blood transfusions or during pregnancy as well as after transplantation.

The traditional determination of antibody specificity is based on the reactivity with HLA antigens such as anti-A1, anti-B7 and anti-DR1 but many antibody reactivity patterns correspond to multiple HLA antigens classified as serologically cross-reacting groups such as the A2-CREG and the B7-CREG. Accordingly, HLA antibodies could be specific for private determinants unique to individual antigens or to public determinants shared by cross-reacting antigens. This experience made us aware that HLA antigens carry multiple serological epitopes but their precise characterization remained elusive. The stereochemical structure of crystallized HLA molecules and determinations of amino acid sequence differences between HLA antigens have made it possible to determine the structural basis of HLA epitopes and their repertoire on the molecular surface. During the past 20 years, many studies with alloantibodies and mouse mAbs have demonstrated that private and public epitopes correspond to distinct

amino acid polymorphisms on the HLA molecular surface. With the realization that HLA antibodies recognize epitopes rather than antigens or CREGs, it has become necessary to develop new criteria to interpret the serum reactivity of sensitized patients. HLAMatchmaker represents an epitope-based approach to assess HLA mismatch acceptability and select suitable donors for alloimmunized patients in need of an organ transplant or requiring matched platelet transfusions [1–3].

A recent review [4**] in *Current Opinion in Immunology* describes the concept of HLAMatchmaker and its usefulness in HLA epitope matching for organ transplantation. There is now widespread support of the usefulness of this algorithm in the clinical setting [5–17]. HLAMatchmaker has been widely used to analyze the serum antibody reactivity patterns of sensitized patients and the identification of potential donors with acceptable mismatches [7–9,18,19]. The application of HLAMatchmaker has enhanced the Acceptable Mismatch program of Eurotransplant for highly sensitized patients [7,9,18].

A dedicated website <http://www.HLAMatchmaker.net> has detailed information and computer programs that can be downloaded free of charge. This review addresses how HLAMatchmaker can increase our understanding of the antibody responses to HLA mismatches.

Brief description of HLAMatchmaker

HLAMatchmaker is a theoretical algorithm whereby each HLA antigen is viewed as a string of amino acid configurations in antibody-accessible positions; they are considered key elements of epitopes that can elicit specific alloantibodies. The original version used triplets, that is, linear sequences of three residues [3], but provided an incomplete description of the HLA epitope repertoire. The so-called eplet version is based on stereochemical modeling of protein antigen–antibody complexes and the contributions of critical amino acid residues that dominate in antigen–antibody binding [1,2]. Antigenic proteins have structural epitopes consisting of 15–22 residues constituting a binding surface of 700–900 Å². Structural epitopes have patches of about 2–5 so-called highly energetic residues (sometimes referred to as ‘hot spots’) that dominate the strength and specificity of binding with antibody. The residues of such functional epitopes are about 3 Å apart from each other and at least one of them is nonself. The remaining residues of a structural epitope contribute supplementary interactions that increase the stability of the antigen–antibody complex. In the new version of HLAMatchmaker, an eplet represents a patch of amino acid residues within a radius of about 3 Å from a polymorphic residue on the HLA molecular surface [1].

Each eplet is assigned a position number in the amino acid sequence and the notation system lists only polymorphic residues marked with the standard letter code. Many eplets are identical to triplets but others have residues in discontinuous sequence positions that cluster together on the molecular surface. Serologically defined HLA determinants correspond well to eplets. The eplet version of HLAMatchmaker represents therefore a more complete repertoire of structurally defined HLA epitopes and provides a more detailed assessment of HLA compatibility.

Class I HLA molecules have 75 polymorphic positions from which we determined 199 eplets on HLA-A, B and C antigens, 110 are on the α helices, 60 are on the side surface and 29 are in less accessible positions at the bottom and under the peptide-binding groove [1]. Class II antigens have 44 DRB, 33 DQB, 29 DQA, 20 DPB and nine DPA polymorphic positions that contribute a repertoire of 146 DRB, 74 DQB, 58 DQA, 45 DPB and 19 DPA eplets [2]. An analysis of 56 major histocompatibility complex class I chain-related gene A (MICA) alleles has identified 38 MICA eplets considered as potential epitopes that can induce specific alloantibodies [20].

HLAMatchmaker applies two principles: each HLA antigen represents a distinct string of structurally defined eplets as potential immunogens that can induce specific

antibodies and patients cannot make antibodies against epitopes that are expressed by their own HLA molecules. The algorithm assesses donor–recipient compatibility through intralocus and interlocus comparisons, and determines which eplets on mismatched HLA molecules are different or shared between donor and patient. An understanding of the HLA antibody response must consider the notion that a mismatched antigen has two characteristics, namely, antigenicity, that is, the reactivity with antibody and, immunogenicity, that is, the ability of inducing an antibody response. Immunogenicity depends on the structural difference between an immunizing protein and the antibody responder’s homologous proteins.

Mismatch immunogenicity and epitope load

HLAMatchmaker can be used as a quantitative tool to determine the degree of a mismatch, that is, the number of mismatched eplets or triplets. A given HLA antigen mismatch has an epitope load that is primarily determined by the recipient’s HLA type representing a repertoire of self-epitopes to which no antibodies can be made. For some patients, a mismatched antigen might be structurally compatible, whereas for other patients, it has multiple mismatched epitopes [4**]. The incidence of the anti-class I antibody response induced by a transplant or during pregnancy correlates with the number of nonself triplets or eplets on mismatched antigens [13,19,21,22]. Minimizing the epitope loads of antigen mismatches is also beneficial in the HLA-based platelet transfusion support of alloimmunized thrombocytopenic patients [15,17].

Conventional criteria consider a DR antigen as a match or a mismatch, but this approach is an insufficient reflection of histocompatibility. Each DR antigen should be viewed as a package of DR+DQ+DP antigens and its class II epitope load depends on the patient’s DR, DQ and DP type. Some DR antigen mismatches have considerable epitope loads at the other class II loci, whereas others appear structurally quite compatible [4**]. Epitope loads also affect anti-class II antibody responses. Donor-specific, DRB1-reactive antibodies are less often detectable than antibodies against other class II epitopes [23]. Antibody absence correlates with low numbers of mismatched DRB1 eplets. In contrast, donor-specific DRB3, 4 and 5 mismatches induce more antibody responses and they have higher numbers of incompatible eplets. Anti-DQ antibodies are rather common and this correlates with more mismatched eplets on DQB and DQA than on DRB1 [23]. Less than one-third of the class II antibodies seem to have anti-DP antibodies reactive with a few DPB eplets and an allelic pair of DPA eplets. Information about epitope loads may permit strategies for HLA mismatch permissibility to prevent or reduce alloimmunization.

Immunogenicity of structurally defined epitopes

There is no reliable structurally based prediction model for determining epitope immunogenicity. Possible factors include location and exposure of an epitope on the molecular surface, the relative differences between the physicochemical properties of amino acid residues and the (HLA) genetic make up of the antibody responder. At present, a practical approach is to collect information about the frequencies of epitope-specific antibody responses in context with the exposure rate to epitope mismatches [24]. This can only be determined if there is sufficient information about the HLA immunogenetic relationship between antibody producer and potential immunizer, and this can be best accomplished with high-resolution (four-digit) molecular typing of all relevant HLA polymorphisms. As a model, we have analyzed HLA antibody specificities of sera from patients with rejected kidney transplants who have undergone allograft nephrectomy. We postulated that donor-specific antibodies are not always detectable in the presence of the transplanted kidney that would absorb them, but they would become readily detectable after the graft has been removed. The first study [25] revealed restricted lymphocytotoxic antibody specificity patterns against certain structurally defined epitopes on immunizing donor HLA class I antigens. Because allograft nephrectomies are uncommonly performed at any transplant center, we initiated a multilaboratory collaboration under auspices of the 14th International HLA Workshop. Although serum screening was limited to lymphocytotoxicity assays and, in some instances, antigen-binding assays such as Elisa and Flow beads, this study yielded promising data showing differences between HLA class I eplet immunogenicity [24].

This collaboration continues during the 15th International HLA Workshop and the antibody screening assays now include the sensitive Luminex assay with single class I and class II alleles. Although our data analysis is still in progress, we have obtained some preliminary data that seem relevant in the clinical setting. This project offers an opportunity to determine how

effective antibody screening on the Luminex platform, which is probably considered the most sensitive assay, is for the detection of circulating donor-specific antibodies before and after allograft nephrectomy (allonx). For 65 cases contributed by 16 laboratories worldwide, we tested pre-allonx and post-allonx sera for donor-specific antibodies in Luminex assays with single HLA alleles (Duquesnoy and Marrari, unpublished observation). In the A, B and DR-matched categories, antidonor antibody reactivity was considerable but less before allonx than after allonx as indicated by significantly lower incidence and strength of positive reactions and lower frequencies of reactive antigens (Table 1). On the contrary, antibodies to donor HLA-C antigens were less common both before and after allonx. Analogous to our previous experience [23], antibodies against donor DRB3/4/5 (DR51/DR52/DR53) mismatches were frequent, but the pre-allonx and post-allonx differences were small and statistically insignificant. Most patients showed HLA-DQ-reactive antibodies, their detection was slightly less in the presence of the allograft, but the difference was not statistically significant. We conclude that even a sensitive assay such as Luminex with single alleles will often yield a limited detectability of antidonor antibodies in the presence of a rejected transplant. This understanding seems relevant to the determination of acceptable mismatches for patients considered for retransplantation.

An HLAMatchmaker-based analysis of antibody reactivity patterns with HLA panels will provide a better understanding how sensitization against a single antigen mismatch leads to antibodies that also react with other antigens, which should be considered as unacceptable mismatches. A recent study [26] addressed the question why sensitization to a DR2 mismatch may lead to antibodies that react also with DR1. This 15th Workshop study was done with 19 informative allonx cases contributed by 13 laboratories worldwide and the data are summarized in Table 2. There were 11 cases with a single DR2 mismatch (DR15 or DR16) and nine of them (82%) showed antibodies reacting also with DR1. Although these antigens might share a distinct epitope recognized by these antibodies, HLAMatchmaker

Table 1 Antidonor HLA class I and class II antibody reactivity before and after allograft nephrectomy

	HLA-A, B and C	HLA-DR	HLA-DQ
Incidence of antidonor antibodies	64 vs. 87% <i>P</i> = 0.0033	57 vs. 86% <i>P</i> = 0.001	76 vs. 87% <i>P</i> = 0.18 (NS)
Strength of antidonor antibodies (median fluorescence intensity values)	7959 ± 5190 vs. 10251 ± 4877 <i>P</i> = 0.0015	9074 ± 5622 vs. 11557 ± 4660 <i>P</i> = 0.0008	9763 ± 5789 vs. 11002 ± 4926 <i>P</i> = 0.13 (NS)
% Reactive donor antigen mismatches	HLA-A, B 49 vs. 75% <i>P</i> < 0.00001 HLA-C 30 vs. 33% <i>P</i> = 0.79 (NS)	DRB1 48 vs. 79% <i>P</i> = 0.0001 DRB3/4/5 65 vs. 78% <i>P</i> = 0.22 (NS)	DQB1 72 vs. 86% <i>P</i> = 0.07 (NS)

NS, not significant.

Table 2 Antibody reactivity of kidney transplant recipients sensitized to DR2 and DR1 mismatches

Immunizer	No. of cases	Reactions with DR2	Reactions with DR51	Reactions with DR1	Reactions with 96EV ^a
DR2-DR51	11	11 (100%)	10 (91%)	9 (82%)	9 (82%)
DR1	8	0 (0%)	8 (100%)	8 (100%)	8 (100%)

^a DR1 and DR51 uniquely share 96EV.

predicts that such structurally defined epitope does not exist. The reactivity with DR1 can be readily explained with antibodies induced by DR51, which is in strong linkage disequilibrium with DR2. DR51 has an epitope defined by the 96EV eplet, which is also shared with DR1 but no other DR antigen. In other words, 96EV on DR51 induced specific antibodies that react also with 96EV on DR1. Conversely, we analyzed eight allonx cases sensitized by a single DR1 mismatch, which has no associated DR51. All of them reacted also with DR51 and this could only be explained with antibodies against the shared 96EV eplet. These findings demonstrate that 96EV represents a highly immunogenic epitope that can induce cross-sensitization between antigens encoded by different DRB loci. It should be noted that none of the DR1 sensitization cases showed antibody reactivity with DR2. Nevertheless, DR2 should be considered indirectly as an unacceptable mismatch because of antibodies to the DR2-linked DR51 through 96EV. This finding illustrates the importance of DRB3/4/5 in determining DRB mismatch acceptability of potential donors.

Our analysis suggests that antibody responses are restricted to a few dominant epitopes on these immunizing DR antigens. For DR2, they are 142M3 (unique for DR2), 71QAA (shared with DB5*02) and 96QV (shared with DR10). DR51 mismatches appear to have three immunogenic eplets: 96EV (shared with DR1), 108T3 (unique for DR51) and 40HFD (shared with DR9). Immunogenic eplets on DR1 are 12LKF2 (unique for DR1), 14FEH (shared with DR9 and DR10) and 25HRL (shared with DR10).

This 15th Workshop project on allograft nephrectomy cases will generate reasonable estimates about epitope immunogenicity following kidney transplantation. Such information will be useful for the development of a donor-selection strategy based on permissible epitope mismatching.

HLAMatchmaker and Terasaki's epitopes

There are two strategies to determine HLA epitopes. HLAMatchmaker is a theoretical model that predicts eplets as critical components of HLA epitopes. The other strategy is based on the analysis of antibody reactivity patterns with HLA panels and the identification of amino acid configurations shared between reactive alleles.

Terasaki's group has done extensive analyses of antibodies tested in Luminex assays with recombinant HLA single antigen beads. These assays were done with mouse mAbs against HLA and anti-HLA alloantibody samples from multiparous women, placentas or patients sensitized by blood transfusions or organ transplants [27]. The allosera were often absorbed with selected HLA recombinant single antigen-expressing cell lines or with microbeads with bound single HLA antigens and the eluates were then tested with HLA panels. These studies have yielded thus far a total of 103 amino acid-defined epitopes on HLA-A, B and C [28], 61 on HLA-DR and 18 on HLA-DQ [29,30]. Two recent comparative studies [31^{**},32^{*}] have determined how Terasaki's epitopes (TerEps) correspond to HLA-Matchmaker-defined eplets. About one-half of class I and about two-thirds of class II TerEps have equivalent eplets (Table 3).

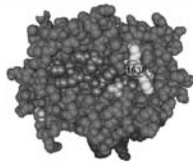

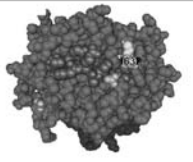
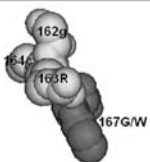
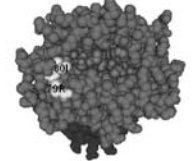

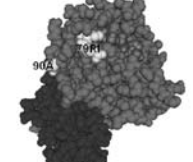
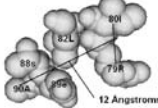
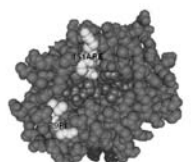
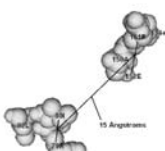
About 10% of class I and 20% of class II TerEps correspond to eplets with permissible residue combinations that do not appear to affect epitope specificity. They reflect a structural cross-reactivity between eplets whereby some residues play a dominant role and other residues have only a minor role in binding with antibody. Structural modeling suggests that these epitopes comprise short sequences of contiguous alignments of dominant and monomorphic residues as potential contact sites for the loops of specificity-determining complementarity-determining regions (CDRs) of antibody. As an example, TerEp #209 is equivalent to the 163RW eplet on A11, A25, A26, A43 and A*6601. Figure 1(a) shows its molecular location on A*1101; 163RW represents a 3-Å patch consisting of the following residues: 162g, 163R, 164c and 166W (monomorphic residues are shown in lower case). TerEp #12 reacts not only with all 163RW-reactive antigens but also with A1 that has a 3-Å patch comprised of 162g, 163R, 164c and 166G. As there are no other amino acid descriptions of TerEp #12, it seems that this epitope is controlled by a dominant 163R residue and 166W and 166G represent permissible substitutions that do not significantly affect the specificity of this epitope. We annotate this eplet as 163R* whereby * represents the permissible 166G/W combination (Fig. 1b). As the specificity-determining CDR loop of antibody interacts with a

Table 3 Numbers of Terasaki's epitopes and their corresponding eplets

HLA locus	Number of TerEps	Equivalent eplets	Eplets with permissible residue combinations	Eplet pairs	No equivalent eplets
ABC	103	50	12	31	10
DRB	60	45	12	3	2
DQ	18	13	3	1	1

TerEps, Terasaki's epitopes.

Figure 1 Example of the structural modeling of Terasaki's epitopes and their equivalent eplet configurations

TerEp	HLA Antigens	Equivalent Eplet	Molecular Configuration	3-Å Patches*
			A*1101	on A*1101
(a) #209	A11,25,26,43,6601	163RW		
(b) #12	A1,11,25,26,43,6601	163R*		
			B*5101	on B*5101
(c) #23	A23,24,25,32; B38,49,51,52,53,57,58,59,63,77	79RI		
(d) #212	A23,24,32; B38,49,51,52,53,57,58,59,63,77	79RI+90A		
(e) #419	B49,51,52,63,77	79RI+152RE		

* Monomorphic residues are shown in lower case.

few contiguous amino acids on antigen, it seems likely that the monomorphic residues in sequence positions 162 and 164 serve as contact sites for antibody.

About 30% of class I TerEps correspond to eplet pairs. This finding extends observations with mAbs that some epitopes are defined by combinations of amino acid configurations separated far enough for contact by two different CDRs of antibody [33–35]. One eplet would function primarily as the specificity recognition site for antibody and the other eplet serves as a critical contact site necessary for binding with antibody and which may comprise a self, a nonself or a locus-restricted sequence.

As an example, TerEp #23 is equivalent to the 79RI eplet shared between Bw4-associated antigens A23, A24, A25, A32, B38, B49, B51, B52, B53, B57, B58, B59, B63 and

B77. Figure 1(c) shows the molecular location of 79RI on B*5101 and its 3-Å patch that has 79R, 80I and 82L. TerEp #212 reacts with the same group of antigens except A25. Apparently, #212 includes 79RI but requires another structural configuration that distinguishes A25 from the other antigens. The only possibility is position 90 whereby A25 has 90D rather than 90A. Thus, #212 corresponds to 79RI+90A and Fig. 1(d) shows the locations of these eplets on B*5101; they are about 12 Å apart. Similarly, we found that #419 on the Bw4-associated B49, B51, B52, B63 and B77 corresponds to the pair of 79RI and 152RE eplets, which are about 15 Å apart (Fig. 1e). TerEp #230 is on another subgroup of Bw4-associated antigens: B38, B49, B51, B52, B53, B59 and B77 and corresponds to two possible eplet pairs 65QIT + 79RI, 71NT + 79RI or both (figure not shown). These findings illustrate that distinct epitopes can

involve the same eplet paired with different eplets within a 15-Å distance.

We identified fewer corresponding eplet pairs for DRB than class I TerEps (Table 3). The number of polymorphic or locus-specific residue positions may explain this difference. Virtually all class I eplet pairs involve the $\alpha 1$ and $\alpha 2$ domains, which have more than 40 such positions. In contrast, there are fewer than 20 polymorphic positions in $\beta 1$ domain of DRB1 and none on the monomorphic DRA. Although both DQA and DQB chains are polymorphic, we identified only one out of 18 DQ TerEps equivalent to an eplet pair. It is possible that the size of the Luminex panel is too small for informative HLA-DQ heterodimers to identify eplet pairs on or shared by DQA and DQB antigens.

We could not identify corresponding eplets for some TerEps (Table 3); several are defined by mouse mAbs and appear to react with xenoepitopes described by residues that are monomorphic for some loci. Conversely, we have identified 38 ABC, 23 DRB and 17 DQ eplets in well exposed surface positions that do not have corresponding TerEps [31^{••},32[•]].

Nevertheless, these TerEp–Eplet comparisons have increased our understanding of HLA epitope immunogenicity (the ability to induce an antibody response) and antigenicity (the ability to react with antibody). HLA-Matchmaker considers an eplet as a key element of an epitope and specific alloantibodies can be induced only if the immunizing HLA antigen presents a nonself eplet that is absent from any antigen of the antibody producer. Sensitization to a mismatched eplet can induce specific antibodies with different reactivity patterns. An antibody may react with:

- (1) All antigens that carry a given eplet that can be expected to interact with its specificity-determining CDR loop.
- (2) Eplet-bearing antigens that share another amino acid configuration about 6–15 Å away and which would serve as a critical contact site for a second CDR loop. Such configuration could be a self-eplet, a nonself eplet or a locus-restricted amino acid sequence.
- (3) Only dominant residues that are present in an eplet, whereas the other residues are permissible combinations that do not significantly alter epitope specificity. Such antibody will react with two or more eplets in the same sequence location provided they share the same dominant residues. Moreover, an epitope may consist of an eplet with permissible residue combinations and which forms a pair with a second eplet or a locus-restricted sequence.
- (4) Eplets whose specific recognition is dependent on nearby hidden residues that alter eplet conformation.

Our experience has shown, however, that such epitopes are rather uncommon.

Conclusion

These concepts are relevant to a better understanding of HLA epitope structure and the interpretation of antibody reactivity patterns with panels of HLA antigens. In the clinical setting, they permit better strategies to identify donors with acceptable mismatches for HLA-sensitized transplant patients and to implement permissible mismatching approaches to reduce allosensitization.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 458).

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