REVEIW

Human leukocyte antigen epitope antigenicity and immunogenicity

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Purpose of review
Human leukocyte antigen (HLA) antibodies are now recognized as being specific for epitopes which can be defined structurally with amino acid differences between HLA alleles. This article addresses two general perspectives of HLA epitopes namely antigenicity, that is their reactivity with antibody and immunogenicity, that is their ability of eliciting an antibody response.

Recent findings
Single-antigen bead assays have shown that HLA antibodies recognize epitopes that are equivalent to eplets or corresponding to eplets paired with other residue configurations. There is now a website-based Registry of Antibody-Defined HLA Epitopes (http://www.epregistry.com.br). Residue differences within eplet-defined structural epitopes may also explain technique-dependent variations in antibody reactivity determined in Ig-binding, C1q-binding and lymphocytotoxicity assays.
HLA antibody responses correlate with the numbers of eplets on mismatched HLA antigens, and the recently proposed nonself-self paradigm of epitope immunogenicity may explain the production of epitope-specific antibodies.

Summary
These findings support the usefulness of HLA matching at the epitope level, including the identification of acceptable mismatches for sensitized patients and permissible mismatching for nonsensitized patients aimed to reduce HLA antibody responses.

Keywords
eplet, human leukocyte antigen antibody, HLA epitope, HLAMatchmaker, nonself-self paradigm of HLA epitope immunogenicity

INTRODUCTION

Human leukocyte antigen (HLA) antibodies are important risk factors for rejection and transplant failure. They are specific for epitopes which can be defined from structural differences between HLA alleles. HLA antigens carry multiple epitopes, and there is increasing experimental support of the concept that donor-recipient compatibility should be assessed at the epitope level.

Current Opinion articles in 2008 and 2009 have described the HLAMatchmaker algorithm and its usefulness in HLA epitope matching and antibody testing for organ transplantation [1,2]. This article addresses in greater detail the antigenicity and immunogenicity of HLA epitopes and their clinical relevance in determining HLA mismatch acceptability and permissibility. Its focus is on HLA class I epitopes recognized by alloantibodies; it does not consider HLA epitopes reacting with alloreactive T-lymphocytes or controlling natural killer cell activity [3].

HLAMATCHMAKER AND STRUCTURAL CONCEPTS OF HLA EPITOPES

As discussed elsewhere [4], an understanding of HLA epitope structure must be based on general concepts how the paratope of antibody binds with a protein epitope. A paratope has three heavy chain and three light chain complementarity determining region (CDR-H1,-H2,-H3,-L1,-L2 and -L3) loops that contact a protein epitope. The interphase consists of multiple amino acid residues distributed over a surface area of 700–900 $Å^2$. There are about 15–25 contact residues in what has been referred to as a

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KEY POINTS

- HLA antibodies are specific for structurally defined epitopes.
- Amino acid differences between epitopes may affect technique-dependent reactivity of HLA antibodies.
- HLA antibody responses correlate with epitope loads of mismatched antigens.
- The nonself-self paradigm of epitope immunogenicity considers an autoreactive component of HLA antibody specificity.
- HLA matching at the epitope level is useful in the clinical transplant setting.

structural epitope and a centrally located so-called functional epitope consisting of a few residues bind with CDR-H3 which plays a dominant role in determining antibody specificity.

HLAMatchmaker considers eplets equivalent to functional epitopes and that they are centrally located within the context of a structural epitope contacted by other CDRs of antibody [4]. On the basis of 700–900Å^2 dimensions of protein epitopes, one can estimate that contacting residues must reside on the HLA molecular surface within a radius of about 15 Å of an eplet. Analogous to functional epitope dimensions, eplets are defined by residue configurations within about 3 Å of polymorphic residues on the molecular surface. Each HLA antigen represents a string of eplets considered key elements of epitopes that elicit specific antibodies. Eplets are annotated by a position number in the amino acid sequence, and polymorphic residues are shown with the standard single letter code. Examples are 62GE (shared between HLA-A2 and HLA-B17), 127K (on HLA-A2, A23, A24, A68 and A69) and 145L (on HLA-B13).

HLAMatchmaker programs consider compatibility and antibody analysis for class I [4], class II [5] and major histocompatibility complex class I-related chain A epitopes [6]. A recent update of the HLA class I epitope repertoire has led to a listing of 270 HLA-ABC eplets on alleles used in Luminex assays for antibody testing, 219 are in antibody-accessible positions on the molecular surface and 51 eplets are defined solely by residue polymorphisms in antibody-inaccessible positions below the molecular surface [7]. This report also addresses issues of the presence of eplets on non-Luminex alleles.

HLA epitopes have two distinct characteristics namely antigenicity, that is their reactivity with antibody, and immunogenicity, that is their ability of inducing an antibody response. In both cases, each eplet must be considered in context with the corresponding structural epitope. These concepts are important not only for a basic understanding of antibody-defined HLA epitopes but are also clinically relevant regarding HLA antibody analysis and assessments of mismatch acceptability and permissibility in organ transplantation.

HLA EPITOPE ANTIGENICITY

HLA epitope antigenicity can be determined by analyzing the reactivity patterns of antibodies with HLA-typed panels. The www.HLAMatchmaker.net website has Microsoft Excel programs to determine epitope specificities of class I, class II and major histocompatibility complex class I-related chain A antibodies. Similar user-friendly EpHLA software has been designed for clinical laboratories and can also assess epitope mismatch acceptability [8,9]. Antibody analysis programs by commercial vendors of Luminex HLA antibody kits also consider epitopes.

To optimize assignments of epitope specificities of antibodies, it is important to incorporate the patient's HLA type (preferably at the four-digit allele level) because this provides information about self epitopes that cannot induce antibodies, whereas other epitopes in the panel would be nonself. The HLA type of the immunizer (for instance, a previous transplant) will identify the mismatched epitopes the patient has been exposed to. This facilitates the identification of antibodies reacting with donor-specific epitopes, which are shared with other alleles in the panel. Third-party epitopes on reactive alleles might be irrelevant unless there is another sensitization event. Although the panels in the antibody assay kits have a limited number of alleles, HLAMatchmaker can also identify antibody-reactive epitopes on the other alleles not included in such panels.

There are many methods to measure serum HLA antibody reactivity, including lymphocytotoxicity, ELISA and flow cytometry. Single allele-binding assays on a Luminex platform have become very popular. These sensitive tests give mean fluorescence intensity (MFI) values as indicators of antibody reactivity. Alleles with high MFI values are interpreted as antibody-reactive and alleles with very low MFI values are considered antibody-nonreactive. Many assay results show alleles with low MFI values that are significantly higher than the MFI values of self-alleles of the antibody producer. Should these alleles be considered antibody reactive or nonreactive? Many histocompatibility laboratories use arbitrary cut-off MFI values (ranging from 500 to 5000) to distinguish between positive and negative reactions. Accordingly, alleles are considered unacceptable or acceptable mismatches and this information is then

incorporated in the selection of transplant donors. We must, however, consider the fact that HLA antibodies recognize specific epitopes and that alleles have structural differences which may affect their reactivity. These considerations will increase our understanding of the wide ranges of MFI values in Luminex panels and on how to interpret alleles as antibody reactive or negative.

HLA antibodies are specific for eplets but certain residue differences between eplet-carrying alleles may affect the reactivity with antibody. As an example, Table 1 summarizes the reactivity patterns of monospecific antibodies specific for twelve 82LR-related epitopes as described in a recently report [10▪]. The website-based HLA Epitope Registry (http://www.epregistry.com.br) has more details of these antibody-verified epitopes. The 82LR eplet corresponds to the Bw4 serological determinant shared between B13, B27 (not B*27:08), B37, B38, B44, B47, B49, B51, B52, B53, B57, B58, B59, B63 and B77 and is also present on A23, A24, A25 and A32.

Monospecific antibodies may have the following reactivity patterns with specific eplet-carrying alleles. First, an antibody has high MFI values with all eplet-carrying HLA alleles including the immunizing allele, whereas the other alleles including self-alleles have extremely low MFI values and thus are nonreactive. Such an antibody is specific for an epitope solely defined by an eplet. Case 1 in Table 1 represents the antibody-verified 82LR eplet shared between all antigens listed in the previous paragraph. It should be noted that both HLA-A and HLA-B mismatches can induce antibodies that react with all 82LR-carrying alleles.

Second, an antibody has high MFI values with certain eplet-carrying alleles (or antigens), including the immunizer but negative MFI values with other eplet-carrying alleles and the other alleles in the panel. Previous studies with class I specific antibodies have shown that the reactive eplet-carrying alleles must have a second polymorphic residue configuration which serves as a critical contact site for antibody [11,12]. Such an antibody is specific for an epitope defined as an eplet pair. Table 1 lists six cases of antibody-verified epitopes defined by 82LR paired with another configuration located within a 15-Å radius. Cases 2, 3, 4 and 5 represent antibody specificities for 82LR+90A, 82LR+144QR, 82LR+145R and 82LR+145RA. Cases 6 and 7 reflect two epitopes: 82LR+138T (on only Bw4-carrying HLA-B antigens) and 82LR+138 M (on A23, A24, A25 and A32) which have been antibody-verified with other antigen-binding assays.

Cases 8 and 9 illustrate how the residue composition in the closely nearby sequence position 80 leads to distinct 82LR-related epitopes. The presence of 80T gives rise to the 80TLR epitope shared between B13, B27, B37, B44 and B47. The other alleles share 80I together with 82LR. This eplet has been annotated as 80I although it includes

Table 1. Reactivity patterns of antibody-verified 82LR-related epitopes recorded in the human leukocyte antigen epitope registry

Case	Reactive epitope	Reactive 82LR-carrying antigens[a]	Nonreactive pairs
1	82LR	All	–
2	82LR+90A	All, except A25	82LR+90D (A25)
3	82LR+144QR	All, except A24 and B13	82LR+144KR (A24) 82LR+144QL (B13)
4	82LR+145R	All, except B13	82LR+145L (B13)
5	82LR+145RA	All, except A25 and B13	82LR+145RT (A25) 82LR+145LA (B13)
6	82LR+138T	Only HLA-B antigens	82LR+138M (HLA-A)
7	82LR+138M	Only HLA-A antigens	82LR+138T (HLA-B)
8	80TLR	B13, B27, B37, B44, B47,	-
9	80I (80ILR)	A23, A24, A25, A32, B38, B49, B51, B52, B53, B57, B58, B59, B63, B77,	-
10	80I+65QI	B38, B49, B51, B52, B53, B59, B77	80I+65GK (A23, A24) 80I+65RN (A25, A32, B57, B58, B63)
11	80I+90A	A23, A24, A32, B38, B49, B51, B52, B53, B57, B58, B59, B63, B77,	80I+90D (A25)
12	80I+151RE	B49, B51, B52, B59, B77	80I+151HV (A24, A25) 80I+151RV (A23, A32, B38, B53, B57, B58)

[a]82LR-carrying antigens: A23, A24, A25, A32, B13, B27 (not B*27:08), B37, B38, B44, B47, B49, B51, B52, B53, B57, B58, B59, B63, B77.

82LR. Cases 10, 11 and 12 represent three antibody-verified epitopes defined by 80I paired with 65QI, 90A and 152RE, respectively.

These findings demonstrate how a given mismatched eplet, in this case 82LR, can induce antibodies with different specificity patterns that depend on a second configuration considered as a critical contact site for antibody binding. Specific eplet-carrying alleles that lack critical contact sites are antibody nonreactive and could be considered acceptable mismatches. Figure 1 shows the molecular locations of critical contact sites. All of them are within a 15-Å radius of 82LR, that is the presumed dimension of the corresponding structural epitope. Position 80 is only 2.6 Å from 82LR, and it seems likely that the same CDR reacts with all these residues. Sequence positions 65–66, 90, 138, 144–149 and 151–152 are far enough from 82LR to make contact with different CDRs of antibody. This structural epitope model illustrates how the reactivity of antibodies with HLA epitopes can involve two separate configurations that can contact separate CDRs.

A third antibody reactivity pattern includes eplet-carrying alleles with low MFI values that are significantly higher than the MFI values of self-alleles of the antibody producer. Such alleles may have distinct residue configurations that interfere with antibody binding but not necessarily cause negative reactions. Table 2 describes four cases with 82LR-specific antibodies, two of them (case 13 and case 14) have similarly high MFI values with all 82LR-carrying antigens, whereas case 15 and case 16 have notably low (but not negative) MFI values with B13, B27, B37, B44 and B47. These antigens have the nearby 80T residue, whereas the reactive antigens, including the immunizing B*51:01 and B*49:01 alleles, have 80I. This suggests that 80T interferes with antibody binding but does not cause a complete block as observed in case 9 (Table 1). The question remains whether B13, B27, B37, B44 and B47 should be considered acceptable or unacceptable mismatches for case 15 and case 16. Our clinical experience has shown many cases whereby certain alleles give low but not negative MFI values patient's antibodies. Often enough, these findings can be explained by considering interfering residues nearby specifically recognized eplets.

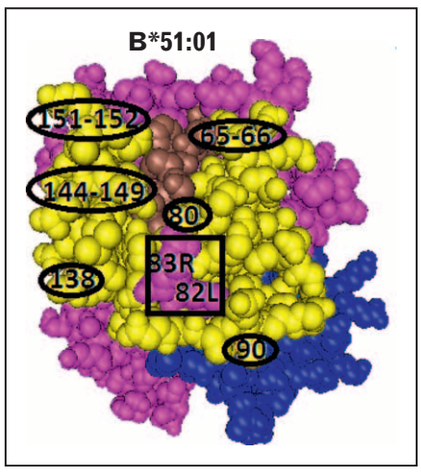

FIGURE 1. Molecular model of the 82LR-defined structure epitope and the locations of residues that play a critical role in determining reactivity with antibodies specific for eplet pairs involving 82LR.

EFFECT OF EPITOPE STRUCTURE ON TECHNIQUE-DEPENDENT HLA ANTIBODY REACTIVITY

Residue differences within eplet-defined structural epitopes may also explain technique-dependent variations in antibody reactivity. Recent studies have compared the reactivity patterns of HLA class I epitope-specific cytotoxic antibodies in Ig-binding, C1q-binding Luminex assays and by complement-dependent lymphocytotoxicity testing with large panels [13▪]. Three reactivity patterns were studied: [1] epitope-carrying alleles reacted equally well in all three assays, [2] some alleles were Ig-binding positive but C1q-binding and CDC were negative and [3] some alleles Ig-binding and C1q-binding were positive but CDC was negative. These technique-dependent reactivity patterns are associated with polymorphic residue variations in structural epitopes of corresponding eplets.

Table 3 has two examples. One monoclonal antibody showed Ig-binding with all 166DG-carrying but gave a very low MFI value in the C1q-binding and no CDC reactivity with A*01:01. This allele had residue differences in positions 62, 67, 152, 156, 158 and 163 in the corresponding structural epitope, some of them must have interfered with the complement-fixing property of this cytotoxic antibody. The second example is a monoclonal cytotoxic antibody with strong Ig-binding and C1q-binding to all 144TKR-carrying alleles except A*80:01 which has an Arg residue in position 151. Therefore, this antibody can be considered specific for an epitope defined by the 144TKR+151H pair. However, only A*11:01 and A*11:02 reacted in CDC; these alleles have a distinct 150AHA combination. It seems that the complement-dependent cytotoxic activity of this antibody requires an interaction with 150AHA in the structural epitope of 144TKR.

These findings can be viewed in the context of the role of multiple CDRs as contact sites for antigen–antibody complex formation [13▪]. Each

Table 2. Influence of residue differences in sequence position 80 on the mean fluorescence intensity values of 82LR-specific antibodies

Allele	Eplet	Residue	Case 13	Case 14	Case 15	Case 16
A*23 : 01	82LR	801	10 483	11 634	2609	12 601
A*24 : 02	82LR	801	8916[a]	11 190[a]	3760	14 744
A*24 : 03	82LR	801	8966	11 210	3633	14 899
A*25 : 01	82LR	801	11 850	13 917	8024	8041
A*32 : 01	82LR	801	11 570	12 411	5050	13 091
B*15 : 13	82LR	801	8736	12 519	4490	6132
B*15 : 16	82LR	801	10 384	14 057	4836	6967
B*38 : 01	82LR	801	12 522	14977	7165	11 071
B*49 : 01	82LR	801	11 240	11 228	6682	13 172[a]
B*51 : 01	82LR	801	8448	13 744	5500[a]	6403
B*51 : 02	82LR	801	11 258	14 186	7297	9178
B*52 : 01	82LR	801	10 274	14 728	6674	7570
B*53 : 01	82LR	801	10 994	14 370	5699	9049
B*57 : 01	82LR	801	10 461	13 501	3217	9968
B*57 : 03	82LR	801	10 132	13 559	2969	9236
B*58 : 01	82LR	801	8695	13 245	2380	8115
B*59 : 01	82LR	801	8664	14 135	5093	7745
		Mean ± SD	10 211 ± 1275	13 212 ± 1272	5004 ± 1751*	9881 ± 2866†
B*13 : 01	82LR	80T	11 531	7171	670	700
B*13 : 02	82LR	80T	12 031	12 628	1081	2651
B*27 : 05	82LR	80T	7684	12 074	779	3690
B*37 : 01	82LR	80T	6007	12 041	1062	2251
B*44 : 02	82LR	80T	12 112	11 722	623	1753
B*44 : 03	82LR	80T	12 149	11 861	685	1860
B*47 : 01	82LR	80T	9968	7935	326	605
		Mean ± SD	10 212 ± 2468	10 776 ± 2231	747 ± 263*	1930 ± 1082†
Self alleles			67	35	13	36

SD, standard deviation. [a]MFI with immunizing allele.
*$P < 0.0001$.
†$P < 0.00001$.

contact results in the release of free energy necessary to stabilize binding and to induce conformational changes in the antibody molecule to expose the C1q-binding site, the first step of complement activation. Moreover, the amount of free energy should be sufficient to induce an additional conformational change of C1q to activate the C1qrs complex as the first stage of the classical complement cascade leading to lymphocytotoxicity. The complement-fixing properties of HLA antibodies require not only specific recognition of eplets but also depend on interactions of other CDRs with critical amino acid configurations within the structural epitope. Eplet-carrying alleles that lack such configurations may only bind with an antibody. This concept is important to our understanding whether or not complement-fixing donor-specific HLA antibodies can initiate antibody-mediated rejection.

IMMUNOGENICITY OF HLA EPITOPES

There are two aspects of the immunogenicity of HLA epitopes, that is, their ability of eliciting antibody responses. Depending on the recipient's HLA type, each donor HLA antigen has a certain number of mismatched epitopes. As previously summarized [2], HLA antibody responses correlate strongly with the epitope loads (i.e., the number of mismatched eplets or triplets) of immunizing antigens and recent publications provide additional experimental support [14–16]. Therefore, epitope loads represent clinically relevant risk factors for antibody-mediated rejection. HLAMatchmaker analysis of the HLA

Table 3. Two examples how residue differences in eplet-defined structural epitopes correlate with antibody reactivity determined in Ig-binding, C1q-binding and complement-dependent lymphocytotoxicity assays

Monoclonal antibody example 1

Allele	Lum-Ig	Lum-C1q	CDC score	Eplet	56	62	65	66	67	69	105	109	131	152	156	158	163
				Sequence positions with residue differences within 15 Ångstroms													
A*01:01	10728	967	1.3	166DG	G	Q	R	N	M	A	P	F	R	A	R	V	R
A*23:01	14354	10530	7.9	166DG	G	E	G	K	V	A	S	F	R	V	L	A	T
A*24:02	13489	3321	7.5	166DG	G	E	G	K	V	A	S	F	R	V	Q	A	T
A*80:01	12911	13013	8.0	166DG	E	E	R	N	V	A	S	F	R	R	L	A	E
B*15:12	14272	4114	8.0	166DG	G	R	Q	I	S	T	P	L	S	E	W	A	L
Other alleles	19	26	1.5	other													

Monoclonal antibody example 2

Allele	Lum-Ig	Lum-C1q	CDC score	Eplet	76	77	79	80	82	83	116	127	150	151	152	156	158
A*11:01	16907	8929	7.0	144TKR	V	D	G	T	R	G	D	N	A	H	A	Q	A
A*11:02	20290	15159	7.5	144TKR	V	D	G	T	R	G	D	N	A	H	A	Q	A
A*01:01	20375	14587	1.2	144TKR	A	N	G	T	R	G	D	N	V	H	A	R	V
A*03:01	22162	16717	1.7	144TKR	V	D	G	T	R	G	D	N	A	H	E	L	A
A*24:02	21608	16188	1.8	144TKR	E	N	R	I	L	R	Y	K	A	H	V	Q	A
A*24:03	20406	19156	1.0	144TKR	E	N	R	I	L	R	Y	K	A	H	V	Q	A
A*36:01	14045	9113	1.0	144TKR	A	N	G	T	R	G	D	N	V	H	A	R	V
A*80:01	13	22	1.0	144TKR	A	N	G	T	R	G	D	N	A	R	R	L	A
Other alleles	31	44	1.1	other													

types of donor and recipient can readily generate this information to be considered in the posttransplant management of nonsensitized patients. Eventually, epitope load information might be incorporated in new strategies to identify donors with HLA permissible mismatches to reduce alloimmunization and increase transplant success.

The second aspect addresses the question: how immunogenic are individual HLA epitopes? Two paradigms have been proposed for HLA epitope immunogenicity. Kosmoliaptsis *et al.* have applied molecular and physiochemical modeling and properties of amino acids, such as hydrophobicity and electrostatic motifs, to assess the immunogenicity of HLA epitopes [17–19]. This issue of *Current Opinion in Organ Transplantation* has a chapter that addresses this concept in greater detail [20].

We have proposed the so-called nonself-self paradigm of HLA epitope immunogenicity [21▪▪]. Our experience with antibody-verified epitopes defined by eplet pairs has shown that the immunizing allele has one eplet that is nonself, whereas as the other part is always a self configuration also present in the HLA type of the antibody producer [11,12]. This suggests that the alloantibody response to an HLA mismatch has an autoreactive component, and this prompted us to consider the nonself-self theory of the immune response originally forwarded by Burnet [22] and extensively discussed and modified by many investigators [23–27].

During B-cell development, rearrangements of V_H and V_L genes produce diversity in the antigen-binding sites of immunoglobulins. These processes lead to the expression of immunoglobulin receptors on developing B-cells which go through several stages to become mature B-cells. These receptors can recognize epitopes on autologous proteins. B-cells with high-avidity receptors disappear after positive and negative selection and receptor editing, and the remaining B-cells carry only low-avidity receptors so that their interactions with autologous proteins will not induce their activation. An antibody response cannot be triggered by every foreign entity, but it requires a 'criterion of continuity' of antigenic patterns (whether endogenous or exogenous) which discriminate nonself from self [26]. In other words, the immune system does not react to self molecules, but will respond to certain modifications within self molecules.

The nonself-self paradigm of HLA epitope immunogenicity is based on the hypothesis that each person had a repertoire of B-cells with low-avidity immunoglobulin receptors for epitopes on their own HLA molecules [21▪▪]. Their interactions with self HLA eplets will not lead to B-cell activation or antibody production. In contrast, exposure to HLA mismatches with nonself eplets may induce alloantibody responses. This means that the remainder of the immunizing structural epitope must be identical or very similar to the corresponding self HLA epitope of the antibody producer.

Three recent reports have provided experimental support for this hypothesis [21▪▪,28,29]. We studied 16 eplet-specific antibodies and in each case, at least one allele of the antibody producer had no or very few differences with the immunizing

allele in antibody-accessible positions defined by a 15-Å radius of the mismatched eplet, the presumed dimension of a structural epitope.

The nonself-self paradigm of HLA epitope immunogenicity may also explain unexpected reactivity patterns of epitope-specific antibodies. Two transplant candidates had antibodies induced during pregnancy against an epitope defined by the 145R+82LR pair on the immunizing B*44:02 [29]. Patient 1 had 145R on her A*30:01, A*66:01 and B*14:02 alleles and patient 2 had 145R on her A*11:01, B*07:02, C*06:02 and C*07:02 alleles. These patients were typed as B*13:02 which has 82LR. In other words, HLAMatchmaker considers both eplets as intralocus and/or interlocus matches which should not induce antibodies in these patients. However, B*13:02 allele has 145L rather than 145R. This would mean that the 145R+82LR pair is different from 145L+82LR, and as an immunogenic epitope it could have activated B-cells with receptors for self 145L+82LR. This conclusion is consistent with the results of comparative sequence analysis which showed that B*13:02 and the immunizing B*44:02 had exactly the same residues within a 15-Å radius of 145L+82LR [29]. There are similar cases whereby the antibody response to an epitope can only be explained with the nonself-self paradigm of HLA epitope immunogenicity (unpublished data).

These findings support the hypothesis that HLA antibodies originate from B-cells with self-HLA immunoglobulin receptors that recognize mismatched eplets in the context with the same or very similar residues in corresponding structural epitopes. It is well known that sensitized patients develop specific antibodies to restricted numbers of mismatched epitopes. The nonself-self paradigm of HLA epitope immunogenicity offers opportunities to explore this phenomenon. It can be postulated that mismatched eplets can induce antibodies only if the other residues in the corresponding structural epitopes are matched with the patient. Conversely, any mismatched eplet with a significantly different structural epitope composition would not be immunogenic and therefore might be considered a permissible mismatch. The nonself-self paradigm of HLA immunogenicity may become clinically useful regarding the prediction of antibody responses to HLA mismatches, but it needs, of course, experimental verification in the clinical setting.

CONCLUSION

Studies of HLA epitope antigenicity can be applied to the serum analysis of serum antibody reactivity of sensitized patients, and this facilitates the identification of suitable donors. Frans Claas *et al.* [30] in Eurotransplant are using this acceptable mismatch approach for highly sensitized patients.

The website-based Registry of Antibody-Defined HLA Epitopes (http://www.epregistry.com.br) is an important recent development [31]. Its goal is to develop a repertoire of HLA epitopes that have been verified by specific antibodies. A recent report summarizes our experience and published data by El-Awar and Terasaki's [32,33] and other investigators with antibody-verified HLA-ABC epitopes [10▪]. There are also reports for HLA-DRDQDP and MICA epitopes [34,35]. HLA professionals are invited to submit data about antibody reactivity patterns specific for newly verified epitopes. The registry is a work in progress and will become a useful resource for investigators interested in HLA matching at the epitope level and in investigating HLA antibody responses in sensitized patients.

Prevention of HLA sensitization represents a challenge for the transplant community. Two causes, namely blood transfusions and the transplant itself, could be approached as being potentially controllable. Perfect HLA matching is somewhat impractical because it can be done for small numbers of patients. For HLA mismatches, information about epitope loads and an understanding of epitope immunogenicity will be useful in assessing risks for sensitization and the clinical management of transplant recipients, especially young patients. Epitope-based permissible mismatching may lead to new strategies to identify suitable donors with minimal risks for allosensitization.

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None.

Conflicts of interest

As the sole contributor of this article Rene Duquesnoy has no conflict of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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