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Second update of the International Registry of HLA Epitopes. I. The HLA-ABC Epitope Database

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A B S T R A C T

The International Registry of HLA Epitopes (http://www.epregistry.com.br) is a website-based resource for HLA epitopes important in transplant rejection and platelet transfusion refractoriness. Its primary goal is to document epitopes that are verified experimentally with specific antibodies. Such epitopes can be defined by single eplets and by eplets paired with certain polymorphic residues within a 15-Å radius, the dimension of the corresponding structural epitope. This report is an update of the HLA-ABC repertoire including descriptions of 72 antibody-verifications of epitopes defined by eplets and/or eplet pairs. The newly updated version 2.0 EpRegistry shows also the polymorphic residue compositions of structural epitopes corresponding to eplets shared between groups of alleles. At present, 151 eplets have not been antibody-verified, and we ranked them with a so-called ElliPro score as a potential predictor of immunogenicity. Sixty eplets with low ElliPro scores might be considered non-epitopes incapable of inducing specific antibodies.

1. Introduction

The International Registry of HLA Epitopes (http://www.epregistry.com.br) was established in 2013 after the 16th International HLA Workshop [1]. EpRegistry serves as a website-based resource for HLA epitopes recognized by antibodies associated with transplant rejection and platelet transfusion refractoriness. So-called eplets are considered essential components of antibody-reactive HLA epitopes and they are defined by molecular modeling and amino acid sequence comparisons within a 3.5-Å radius of polymorphic residues on the HLA molecular surface [2]. Eplets are theoretical considerations and EpRegistry has eplet repertoires for HLA-ABC, HLA-DRB1/3/4/5, HLA-DQ, HLA-DP and MICA.

The primary goal of EpRegistry is to identify epitopes that are verified experimentally with specific antibodies. Such epitopes correspond to individual eplets or to eplets paired with other amino acid configurations shared between reactive alleles. The first update published in 2014 [3] described 62 HLA-ABC antibody-verified epitopes that correspond to eplets, including 33 defined by eplets paired with other residue configurations.

This report describes a version 2.0 update of the HLA-ABC repertoire in EpRegistry, including new features about antibody-verified and non-verified eplets.

2. Methods and results

EpRegistry descriptions of antibody-verified eplets originally distinguished between “confirmed” and “provisional” status. The second update included a reevaluation of each antibody reactivity pattern used for epitope verification, especially those cases with a provisional status. This analysis has led to the exclusion of the antibody verification of three eplets (66NV, 66IF, 113H) because the interpretations were made for sera with complex reactivity patterns and no absorption-elution analyses were done with informative alleles. EpRegistry has also recent additions of newly antibody-verified eplets with antibody reactivity patterns described in recent publications [4–9].

As of August 1, 2018, EpRegistry has records of 72 HLA-ABC eplets that have been verified with antibodies (Table 1), either as eplets alone and/or paired with other amino acid configurations. Arbitrary assignments of “Confirmed” or “Provisional” status have been removed. For most antibody-verified eplets, EpRegistry provides detailed evidence about variations of antibody reactivity patterns associated with single eplets and/or eplets paired with other residue configurations within the structural epitope concept. EpRegistry is a work-in-progress and will be updated continually when new data become available.

After a five year-existence of EpRegistry, we must conclude that many eplets have not been experimentally verified with specific antibodies. How many of them have the potential of being antibody-reactive and conversely, which eplets are represented by amino acid configurations that can never elicit specific antibody responses? Amino acid residues that can never be a part of any antigenic epitope complexed with antibody are referred to as non-epitope residues [10]. A distinction between epitopes and non-epitopes is important in vaccine designs and the generation of specific antibodies used in immunotherapy and immunodiagnostics [11,12]. Although there are many B-epitope prediction programs, we have found one easily

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Table 1
Seventy-two antibody-verified HLA-ABC eplets in the Registry (as of August 1, 2018).

Eplet	Residues	ElliPro	SAB Antigens and Alleles
21H	21H	0.404	C2,C3,C*04:03,C15
41T	41T	0.922	B13,B40,B41,B12,B47,B21
44KM	44K45M (150VHA) (158V)	0.470	A1,A36
44RMA	44R45M46A	0.439	B13,B*15:01/02/11/12/13/16,B46,B57
44RT	44R45T	0.514	B18,B35,B37,B5,B53,B58,B78
45KE	45K46E	0.372	B40,B41,B12,B47,B21
56R	56R	0.836	A30,A31
62EE	62E63E	0.444	A23,A24,A80
62GE	62G63E	0.375	A2,B17
62GK	62G66K	0.362	A2
62GRN	62G65R66N	0.423	B17
62LQ	62L63Q	0.390	A29,A43
62QE	62Q63E	0.382	A1,A3,A11,A30,A31,A32,A36,A74
62RR	62R65R	0.532	A25,A26,A33,A34,A66,A28,B*15:16
65GK	65G66K	0.341	A23,A24
65QIA	65Q66I69A	0.362	B*07:02,B27,B42,B22,B67,B73,B81,B82
65QKR	65Q66K69R	0.381	B46,C1,C2,C3,C4,C5,C6,C*07:02/04,C8,C12,C14,C16,C17,C18
65RNA	65R66N69A	0.370	A1,A3,A11,A25,A26,A29,A30,A31,A32,A33,A*34:02,A36,A43,A66,A28,A74,A80,B*15:16,B17
69AA	69A71A	0.306	B*07:02,B*15:16,B27,B42,B22,B17,B67,B73,B81,B82
69TNT	69T70N71T	0.288	B*07:03,B8,B13,B14,B*15:01/02/03/10/11/12/13,18,B18,B35,B37,B16,B40,B41,B12,B47,B48,B21,B5,B53,B59,B78
70IAQ	66I69A70Q	0.230	B*07:02,B42,B22,B67,B81,B82
71ATD	71A73T77D	0.334	B*27:03/05
71SA	70S71A	0.245	B*15:16,B17
71TTS	71T73T77S	0.343	B*07:03,B8,B14,B*15:01/02/03/10/11/12/18,B18,B35,B39,B40,B41,B45,B48,B50,B78
73AN	73A77N	0.328	C4,C6,C17,C18
73TVS	73T76V77S	0.400	B46,C1,C3,C8,C14,C16
76ANT	76A77N80T	0.518	A1,A26,A29,A36,A43,A80
76EG	76E79G	0.630	A*30:02
76ESI	76E77S80I	0.522	A25,A32
76ESN	76E77S80N	0.527	B7,B8,B14,B*15:01/02/03/10/11/12/18,B18,B*27:08,B35,B39,B40,B41,B42,B45,B48,B50,B22,B67,B78,B81,B82
76VRN	76V79R80N	0.634	B46,B73,C1,C3,C7,C8,C12,C14,C16
79GT	79G80T	0.669	A1,A2,A3,A11,A26,A29,A30,A31,A33,A34,A36,A43,A66,A28,A74,A80
80I	80I	0.635	A23,A24,A25,A32,B*15:13,B*15:16,B38,B49,B5,B53,B17,B59
80K	80K	0.648	C2,C4,C5,C6,C15,C17,C18
80N	80N	0.650	B7,B8,B14,B*15:01/02/03/10/11/12/18,B18,B*27:08,B35,B39,B40,B41,B42,B45,B46,B48,B50,B22,B67,B73,B78,B81,B82,C1,C3,C7,C8,C12,C14,C16
80TLR	80T82L83R	0.781	B13,B*27:03/05,B37,B44,B47
82LR	82L83R	0.854	A23,A24,A25,A32,B13,B*15:13/16,B*27:03/05,B37,B38,B44,B47,B49,B5,B53,B17,B59
90D	90D	0.944	A1,A11,A25,A26,A34,A36,A43,A*66:01,A80,B73,C4,C6,C7,C18
107W	107W	0.591	A2,A69
127K	127K	0.593	A2,A23,A24,A28
131S	131S	0.747	B13,B14,B15,B18,B27,B35,B37,B16,B12,B46,B47,B21,B5,B53,B22,B17,B59,B67,B78,B82
138K	138K	0.916	C5,C*08:02
138MI	138M142I	0.865	A1,A3,A11,A23,A24,A25,A26,A29,A30,A31,A32,A33,A34,A36,A43,A66,A74,A80
143S	143S	0.557	B*40:01,B48,B81,C17
144K	144K	0.736	A1,A2,A3,A11,A24,A36,A28,A80
144KR	144K145R	0.817	A1,A3,A11,A24,A36,A80
144QL	144Q145L	0.810	B13
144TKH	142T144K145H	0.807	A2,A28
145KHA	144K145H149A	0.825	A*02:01/02/05/06,A28
145RT	145R149T	0.875	A25,A26,A34,A43,A66
149TAH	149T150A151H	0.787	A*02:03A25,A26,A34,A43,A66
150AAH	149A150A151H	0.787	A*02:01/02/05/06,A3,A11,A24,A28
151AHA	150A151H152A	0.655	A11
156DA	156D158A	0.401	B8,B37,B41,B42,B*44:02,B45,B82,C*07:04
158T	158T	0.544	B16,B67
161D	161D	0.588	A3
163EW	163E167W	0.385	A*66:02,B7,B13,B27,B*40:01/02/06,B47,B48,B73,B81,C2,C17
163LS/G	163L167S/G	0.399	B*15:12,B12,B82
163LW	163L167W	0.401	B*15:01/02/03/10/11/13/16/18,B35,B*40:05,B46,B21,B5,B53,B56,B17,B78,C3
163R	163R	0.489	A1,A11,A25,A26,A43,A*66:01
163RG	163R167G	0.416	A1
163RW	163R167W	0.447	A11,A10,A43,A*66:01
166DG	166D167G	0.469	A1,A23,A*24:02,A80,B*15:12
173K	173K	0.783	C3
177KT	177K178T	0.542	C5,C*07:04,C8
180E	180E	0.455	B7,B8,B*40:01,B41,B42,B48,B81
193PL	193P194L	0.945	C7
193PV	193P194V	0.946	B35,B5,B53,B58,B78,C1,C2,C3,C4,C5,C6,C8,C12,C14,C15,C17,C18
219W	219W	0.921	C1,C3,C4,C14,C18
248M	248M	0.836	C1
253Q	253Q	0.941	A2,A25,A26,A29,A31,A32,A33,A34,A43,A66,A28,A74,B73,C7,C17
267QE	267Q268E	0.705	B73,C7,C17

Table 2
Polymorphic residue differences between 82LR-carrying alleles.

Residue Differences within 15 A											
	Eplet	12	71	77	80	81	90	138	144	145	149
A*23:01	82LR	V	S	N	I	A	A	M	Q	R	A
A*23:02	82LR	V	S	N	I	A	A	M	Q	R	A
A*24:02	82LR	V	S	N	I	A	A	M	K	R	A
A*24:03	82LR	V	S	N	I	A	A	M	K	R	A
A*25:01	82LR	V	S	S	I	A	D	M	Q	R	T
A*32:01	82LR	V	S	S	I	A	A	M	Q	R	A
B*13:01	82LR	M	T	N	T	A	A	T	Q	L	A
B*13:02	82LR	M	T	N	T	A	A	T	Q	L	A
B*15:13	82LR	M	T	N	I	A	A	T	Q	R	A
B*15:16	82LR	M	A	N	I	A	A	T	Q	R	A
B*27:03	82LR	V	A	D	T	L	A	T	Q	R	A
B*27:05	82LR	V	A	D	T	L	A	T	Q	R	A
B*37:01	82LR	V	T	D	T	L	A	T	Q	R	A
B*38:01	82LR	V	T	N	I	A	A	T	Q	R	A
B*44:02	82LR	M	T	N	T	A	A	T	Q	R	A
B*44:03	82LR	M	T	N	T	A	A	T	Q	R	A
B*47:01	82LR	M	T	D	T	L	A	T	Q	R	A
B*49:01	82LR	M	T	N	I	A	A	T	Q	R	A
B*51:01	82LR	M	T	N	I	A	A	T	Q	R	A
B*51:02	82LR	M	T	N	I	A	A	T	Q	R	A
B*52:01	82LR	M	T	N	I	A	A	T	Q	R	A
B*53:01	82LR	M	T	N	I	A	A	T	Q	R	A
B*57:01	82LR	M	A	N	I	A	A	T	Q	R	A
B*57:03	82LR	M	A	N	I	A	A	T	Q	R	A
B*58:01	82LR	M	A	N	I	A	A	T	Q	R	A
B*59:01	82LR	M	T	N	I	A	A	T	Q	R	A

accessible program that appears effective to assess eplet immunogenicity.

ElliPro (derived from Ellipsoid and Protrusion) is a structurally based epitope predictor software program developed by Ponomarenko [13,14]. ElliPro is available on the website-based Immune Epitope Database (www.iedb.org) [15,16] and can assign a protrusion score for each residue on an antigenic protein and identify epitope locations with clusters of residues with high ElliPro scores. We have recently determined the ElliPro scores of amino acid residues on different HLA molecules [17]. Our analysis focused on polymorphic residues in eplets that can be considered as driving forces for specific antibody responses. The ElliPro scores were much higher for antibody-verified eplets than eplets without antibody verification; median values: 0.576 versus 0.223 ($p = 1.1 \times 10^{-12}$). This study demonstrates the usefulness of ElliPro scores in assessing the immunogenicity of HLA-ABC eplets.

Table 1 shows the average ElliPro scores for the residues defining each antibody-verified eplet and there are lists of eplet-carrying reactive alleles in commonly used single allele bead (SAB) panels used for Luminex HLA antibody screening. Although EpRegistry displays only alleles rather than antigens, Table 1 becomes easier to read with serological specificities shown if all their associated alleles share the eplet. For instance, 62GE is on A2 represented by A*02:01, A*02:02, A*02:03, A*02:05 and A*02:06. This eplet is also on B*57:01, B*57:03 and B*58:01 but Table 1 shows B17 which is equivalent to the B57 and B58 serological splits. The SAB panel has two C4 alleles: C*04:01 and C*04:03, but the 21H eplet is only on C*04:03.

EpRegistry has eplet descriptions for a large panel of 587 HLA-A, 980 HLA-B and 332 HLA-C alleles; these alleles are shown in Supplemental Table 1. This information is useful in determining for sensitized patients which alleles outside the SAB panel can be considered unacceptable mismatches because they carry eplets specifically recognized by patient's antibodies. This repertoire of alleles should be considered incomplete and there are two additional limitations about determinations of mismatch acceptability. First, 1017 of these alleles lack amino acid sequence information in the alpha 3 domain (sequence positions 183–285), so it is impossible to assess any matching of eplets located in that part of the HLA molecule. Second, certain non-SAB alleles may have eplets such as 62PE (on B*40:29 and B*44:32) and 75Q (on B*15:148 and B*40:66) absent from the SAB panel repertoire; such eplet-specific antibodies would not be detected in patient's serum. EpRegistry does not include descriptions of these eplets.

The original HLA-ABC eplet repertoire included eplets in overlapping sequence positions and several are defined by the same polymorphic residue together with one or two residues that are monomorphic at other class I loci. Since a polymorphic residue can be considered the driving force for an antibody-inducing eplet we decided to combine the eplet designations into one eplet described solely by that polymorphic residue. For instance, the redundancy of 62REN, 62RTN, 63EN, 65QNR and 66NAQ have been reduced to a single eplet designated as 66N because residues 62R, 63E, 64T, 65Q, 69A, 69R and 70Q are monomorphic for at least one class I locus. Similarly, eplets 69ATN, 71ATN, 71STN, 73TN and 73TVN have been combined as the 77N eplet because 69A, 71A, 71S, 73T, 76V are monomorphic at other loci. These redefinitions have reduced the number of eplets without antibody verification from 204 to 151. The latter have been grouped according to their ElliPro scores. Supplemental Table 2 summarizes these changes.

Supplemental Table 3 shows 60 eplets with low scores that are below 0.250 and 37 of them have very low scores under 0.150. These eplets might be considered as non-epitopes incapable of inducing specific antibodies, but additional studies are needed to conclude that they are not immunogenic.

The remaining 91 eplets have ElliPro scores higher than 0.250 (Supplemental Table 4). Twenty-eight eplets have intermediate ElliPro scores (0.250–0.399), 63 eplets have scores of 0.400 or higher. These eplets might be considered the best candidates for antibody-verification, but it should be noted that certain eplets are only present on low frequency alleles (e.g. 163LG on B*15:12 and 184R on C*17:01) or on large groups of alleles including 62RN, 66K and 163T. Such eplets are unlikely to be mismatched and specific antibodies will rather be uncommon.

The updated Registry has also links to display polymorphic residue descriptions of structural epitopes identified within a 15-Å radius for many eplets shared by groups of alleles commonly tested in Luminex assays. This residue information about structural epitopes is helpful in identifying antibodies specific for epitopes defined by eplets paired with other residue configurationsAs an example, let us look at the polymorphic residue differences between alleles carrying the 82LR eplet; they involve 10 sequence locations within a 15-Å radius (Table 2) Many antibodies react specifically with all alleles carrying the Bw4-assocated 82LR, but other antibodies have shown more restricted reactivity patterns that can only be explained by the presence of distinct residues. Examples are 82LR + 90A (A25 is non-reactive), 82LR + 138M (only on 82LR-carrying HLA-A alleles) and 82LR + 144QR (A24 and B13 are non-reactive). Table 2 shows also residues such as 12V, 12M, 71S, 71T, … etc. that can pair with 82LR; such pairs have (yet) not been verified with specific antibodies. Polymorphic residue descriptions of structural epitopes provide opportunities to analyze the variations between eplet-associated antibody reactivity patterns.

3. Discussion

The 2018 version 2.0 update of the HLA-ABC epitope registry has several major modifications. First, each antibody verification report combines the evidence about antibody specificities associated with eplets shared by all reactive alleles and with eplets paired with other residue variations. This new reporting format is intended to demonstrate the variability between reactivity patterns of antibodies induced by a given mismatched eplet.

Such variability reflects the fact that epitopes interact with the different Complementarity Determining Regions (CDRs) of the antibody paratope: H1, H2 and H3 are on immunoglobulin heavy chains and L1, L2 and L3 are on light chains. It is well known that CDR-H3 plays a central role in determining antibody specificity towards epitopes on

protein antigens; it recognizes so-called functional epitopes, small configurations of amino acid residues residing within a radius of 3–3.5 Å. So-called eplets correspond to functional epitopes and HLA molecular modelling and sequence analyses have defined eplet repertoires.

Many antibodies react only with all HLA alleles sharing the same eplet with the immunizing allele, whereas others react with a subgroup of HLA alleles that share a distinct additional amino acid configuration with the immunizing allele. Such a configuration serves as a critical contact site and is located within 15 Å of the eplet, i.e. within the dimensions of a structural epitope contacting other CDRs of the antibody paratope.

Thus, a given mismatched eplet on an immunizing allele can induce specific antibodies reacting differently with eplet-carrying HLA alleles, and HLAMatchmaker antibody analysis programs (downloadable from www.epitopes.net) can identify amino acid residue configurations associated with such reactivity variations. The antibody verification reports in EpRegistry illustrate how different antibody reactivity patterns can be induced by the same mismatched eplet in combination with other residues that must be shared between the immunizing allele and the reactive alleles in the panel. Under the structural epitope heading, the updated Registry now shows for each eplet on a group of alleles, which residues are different within a radius of 15 Å. This information is a useful guide for addressing the question why certain antibodies react with the immunizing eplet-carrying allele but not with all eplet-carrying alleles in the panel. We invite HLA laboratories to submit documentation of any complexity of eplet-induced antibody reactivity patterns.

Second, the HLA-ABC eplet repertoire has been simplified by combining overlapping eplets associated with the same polymorphic residue in a given sequence position if the other residues in the eplet description were monomophic at one or more HLA-A/B/C loci. Polymorphic residue differences can be considered the driving force for an antibody response which, of course, depends on the immunogenicity of the eplet.

The third modification of EpRegistry addresses the issue that many eplets in the HLA-ABC repertoire have never been experimentally verified with specific antibodies. This lack of verification can be explained by the possibility that certain eplets can induce antibodies that have not (yet) been identified and conversely, that other eplets are non-immunogenic because they reflect so-called non-epitopes incapable of inducing specific antibodies. As summarized above, a structurally based B-cell epitope prediction algorithm has shown that antibody-verified eplets have polymorphic residues with much higher ElliPro scores than eplets that have not been antibody-verified [17]. This information has been applied to EpRegistry by classifying non-verified eplets according to their ElliPro scores. Eplets with very low and low scores are predicted to have no or little immunogenicity. Although it is still a *non sequitur* to conclude that the inability to identify specific antibodies reflects the fact that such eplets are non-epitopes, we anticipate their eventual removal from EpRegistry.

Eplets with intermediate and high ElliPro scores might be considered as candidates for antibody-verification. This information can serve as a guide for HLA laboratories interested in analyzing new antibody reactivity patterns that cannot be explained with the current antibody-verified eplets or pairs. We welcome their contributions.

Similar updates will be implemented for the class II (HLA-DR, DQ, DP) and MICA eplet databases in the EpRegistry. We have already recorded the ElliPro scores for these eplets, as well as indicating the antibody-verified status in the same way as was done for class I in Version 2.0. A manuscript is currently in preparation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2018.11.007.

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