Human Immunology 75 (2014) 1097–1103

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

First report on the antibody verification of HLA-DR, HLA-DQ and HLA-DP epitopes recorded in the HLA Epitope Registry

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ARTICLE INFO

Article history:
Received 1 February 2014
Accepted 25 September 2014
Available online 13 October 2014

Keywords:
HLA epitopes
HLA-DRB epitopes
HLA-DQ epitopes
HLA-DP epitopes

ABSTRACT

The International Registry of Antibody-Defined HLA Epitopes (http://www.epregistry.com.br) has been recently established as a tool to understand humoral responses to HLA mismatches. These epitopes can be structurally defined as eplets by three-dimensional molecular modeling and amino acid sequence differences between HLA antigens. A major goal is to identify HLA eplets that have been verified experimentally with informative antibodies. This report addresses class II epitopes encoded by genes in the HLA-D region. Our analysis included reviews of many publications about epitope specificity of class II reactive human and murine monoclonal antibodies and informative alloantibodies from HLA sensitized patients as well as our own antibody testing results. As of July 1, 2014, 24 HLA-DRB1/3/4/5, 15 DQB, 3 DQA and 8 DPB antibody-verified epitopes have been identified and recorded. The Registry is still a work-in-progress and will become a useful resource for HLA professionals interested in histocompatibility testing at the epitope level and investigating antibody responses to HLA mismatches in transplant patients.

1. Introduction

It is now well recognized that antibodies to HLA class II mismatches can induce allograft rejection and transplant failure. Such antibodies recognize epitopes which can now be defined structurally by HLA molecular modeling and amino acid sequence comparisons. Under auspices of the 16th International Histocompatibility and Immunogenetics Workshop we have developed a website (<http://www.epregistry.com.br>) for the International Registry of HLA Epitopes [1]. Its goal is to document a repertoire of HLA epitopes that have been identified with specific antibodies and therefore might be clinically relevant. The Registry has five epitope databases: HLA-ABC, HLA-DR, HLA-DQ, HLA-DP and MICA. Each database is a list of potential epitopes annotated as eplets which are small configurations of polymorphic amino acid residues in sequence locations on the HLA molecular surface.

In the 1980s the mapping of genes in the HLA-D region led to extensive research efforts on antibody-defined class II polymorphisms. These studies utilized a variety of class II-specific antibodies and analyses of immunoprecipitated class II molecules from cell lines with mutated genes as well as DNA analysis provided detailed information about the gene organization of HLA-D. Moreover, lymphocytotoxicity testing permitted a serological definition of DR and DQ antigens. However, many class II specific antibodies have complex reactivity patterns presumably against antigenic determinants (or epitopes) shared between multiple class II antigens. Some early reviews indicated already that such epitopes correlate with amino acid polymorphisms [2–4] and many subsequent publications have addressed amino acid descriptions of antibody-defined class II epitopes. During recent years, the availability of more sensitive antibody detection techniques especially Luminex-based assays with single alleles, has enhanced the determination of epitope specificities of HLA antibodies. This is the first report on class II epitopes which have been verified with informative antibodies and recorded in the Registry. It reflects a comprehensive analysis of the literature on antibody-defined class II

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http://dx.doi.org/10.1016/j.humimm.2014.09.012
0198-8859/

epitopes as well as data in our laboratories. Other reports describe antibody-verified HLA-ABC and MICA epitopes recorded in the Registry [5,6].

2. Methods

The http://www.epregistry.com.br website has three class II epitope databases: DRB1/3/4/5, DQB + DQA and DPB + DPA [1]. Epitopes are recorded as amino acid residue configurations (eplets) determined by molecular modeling of HLA structures and residues within 3 Ångstroms of surface-exposed polymorphic residues [7]. Eplets are considered essential elements of antibody-defined HLA epitopes and they are annotated by distinct sequence position numbers and residue descriptions with standard single letter amino acid codes. The Registry lists 143 DRB1/3/4/5, 58 DQB, 25 DQA, 45 DPB and 15 DPA eplets and this report describes eplets which have been verified so far with informative specific antibodies.

Our analysis considered reactivity patterns of HLA class II specific antibodies reported in many research papers, review articles and international HLA workshop reports. Informative antibodies (human and murine monoclonal antibodies (mAbs) and monospecific allosera and eluates of absorbed sera) have been tested with differently sized HLA panels tested in various antibody-binding assays such as Luminex, Flow cytometry and ELISA as well as complement-dependent lymphocytotoxicity. Serological testing was done with peripheral blood B-cells (PBL) and transformed B lymphoblastoid cell lines (B-LCL) generally from HLA homozygous donors. Serological data addressed the distinction between antibody-reactive and nonreactive antigens or alleles, and often enough, apparently monospecific antibodies showed high correlation values ($r > 0.85$) with one antigen or a distinct group of antigens or alleles. In such instances we have used the HLAMatchmaker algorithm to determine what epitopes might be recognized by such antibodies. Many basic research investigations addressed the effects of class II gene manipulations such as cross hybridization and site mutagenesis as well as antibody reactivity of transfected cells with mutated HLA alleles that had informative amino acid residue substitutions. They have provided additional insights about the structural basis of certain antibody-defined HLA epitopes.

Antibody-verified epitopes can be classified as "confirmed" or "provisional" depending on the amount of information available in terms of how often specific antibodies have been identified and the completeness of reactivity patterns with informative class II panels. Special consideration has been given to allosensitization-induced human mAbs and the reactivity of eluates of selectively absorbed allosera as well as the antibody reactivity with mutated alleles. Future studies may permit upgrades from "provisional" to "confirmed" status if additional experimental support becomes available. Conversely, there could be downgrades to "questionable" status if new data contradict previous interpretations.

3. Results

As of July 1, 2014 a total of 50 antibody-verified HLA class II epitopes has been recorded in the Registry. Their presence is listed on single class II allele beads commonly used in antibody assays on a Luminex platform. Table 1 has antigen descriptions of these alleles. This report lists antigens if a given antibody-verified epitope is present on all corresponding Luminex alleles; for instance DR1 is shown if DRB1*01:01, DRB1*01:02 and DRB1*01:03 have the epitope. On the other hand, alleles are listed if the epitope is on one or some of them. The Epitope Registry website shows for each epitope the alleles in Luminex panels as well as a complete list of all alleles.

Tables 2–4 list the class II epitopes which have been verified so far with informative antibodies; an asterisk indicates a provisional status. Each epitope has a polymorphic residue description and a list of eplet-carrying antigens and/or alleles present on single antigen beads commonly used in antibody assays on a Luminex platform. The following descriptions indicate the antibody sources and methods that have been used for antibody-verified epitopes: A, alloserum; E, alloserum eluate; H, human mAb; M, mouse mAb; and S, site mutagenized alleles with residue substitutions. The cited relevant publications are also listed. The tables in this report represent only summaries of our analysis. The http://www.epregistry.com.br website has more detailed documentation about antibody-verified epitopes and their expression on Luminex and non-Luminex alleles.

3.1. Antibody-verified HLA-DRB epitopes

Twenty-four DRB1/3/4/5 epitopes have been verified so far with informative antibodies (Table 2). Their molecular locations range from sequence position 4–181 and all are expressed on the molecular surface. Some antibody-verified DRB epitopes are uniquely expressed by single alleles in the Luminex panel and others reside on multiple antigens encoded by DRB1 or combinations of DRB1/3/4/5 loci.

Table 1
Antigen descriptions of class II alleles on single antigen beads commonly used in antibody assays on a Luminex platform.

Antigen	Allele	Antigen	Allele	Antigen	Allele
DR1	DRB1*01:01/02/03	DQ2	DQB1*02:01/02	DP1	DPB1*01:01
DR3	DRB1*03:01/02/03	DQ3	DQB1*03:01/02/03	DP2	DPB1*02:01/02
DR4	DRB1*04:01/02/03/04/05	DQ4	DQB1*04:01/02	DP3	DPB1*03:01
DR7	DRB1*07:01	DQ5	DQB1*05:01/02/03	DP4	DPB1*04:01/02
DR8	DRB1*08:01	DQ6	DQB1*06:01/02/03/04/09	DP5	DPB1*05:01
DR9	DRB1*09:01/02	DQ7	DQB1*03:01	DP6	DPB1*06:01
DR10	DRB1*10:01	DQ8	DQB1*03:02	DP8	DPB1*08:01
DR11	DRB1*11:01/04	DQ9	DQB1*03:03	DP9	DPB1*09:01
DR12	DRB1*12:01/02	DQA1	DQA1*01:01/02/03/04	DP10	DPB1*10:01
DR13	DRB1*13:01/03	DQA2	DQA1*02:01	DP11	DPB1*10:01
DR14	DRB1*14:01/02/54	DQA3	DQA1*03:01/02/03	DP13	DPB1*13:01
DR15	DRB1*15:01/02/03	DQA4	DQA1*04:01	DP14	DPB1*14:01
DR16	DRB1*16:01/02	DQA5	DQA1*05:01/03/05	DP16	DPB1*16:01
DR51	DRB5*01:01/02:02	DQA6	DQA1*06:01	DP17	DPB1*17:01
DR52	DRB3*01:01/02:01/02:02/03:01	DPA1	DPA1*01:03/04/05	DP18	DPB1*18:01
DR53	DRB4*01:01/03	DPA2	DPA1*02:01/02	DP19	DPB1*19:01
		DPA3	DPA1*03:01	DP23	DPB1*23:01
		DPA4	DPA1*04:01	DP28	DPB1*28:01

Table 2
Current listing of antibody-verified HLA-DRB1/DRB3/DRB4/DRB5 epitopes.

DRB Epitope*provisional	Polymorphic residue descriptions	Epitope-carrying antigens and/or alleles in Luminex kits	Verified with[a]	References
4Q	4Q	DR7, DR9, DR53	A, M, S	[8–13]
4R*	4R	All DRB antigens except DR7, DR9, DR53	M, S	[3,11,14]
11STS*	11S12T13S14E	DR3, DR11, DR13, DR14	A, M	[13,15,16]
16Y	16Y13G	DR8, DR12	A, H, M	[12,16,17]
$25Q_3$	25Q26F 12K13Y14K 70D71R73G74Q	DR7	A, M, S	[12,16,18–20]
25R	25R	All DRB antigens except DR7 and DR53	A, M, S	[3,18–23]
37YV*	37Y38V	DR4, DR8, DR11 and DRB1*13:03	H	[24–26]
$48Q_6$	48Q 25W26N 18L 40Y41N44L 81Y180M	DR53	A, H, M	[8,18,19,27]
51R	51R	DRB3*02:01/02	A, H, M	[23,28,29]
57DE	57D58E	DR11	A, H, M, S	[3,9,12,16,18,23,30,31]
$57DE^{DP}$	57D58E or 55D56E on DP	DR11 shared with DP1*02:01, DP3, DPB1*04:02, DP6, DP9, DP10, DP14, DP16, DP17, DP18, DP28	A, H, M, S	[16,30–34]
70QT*	70Q77T	DR1,DRB1*04:01/03/05, *14:02, DR15 and DRB5*02:02	M, S	[22,35,36]
73A*	73A77T	All DRB except DR3, DR7 and DR52	M, S	[11,37]
74R	70Q73G74R	DR3, DRB3*01:01	A, H, M	[3,23,29]
77N	73G77N78Y	DR3, DR52	A, M, S	[12,15,29,38,39]
77T	77T	All DRB antigens except DR3 and DR52	A, M, E, S	[13,38,40,41]
96EV	96E98K180V	DR1, DR51	A, M	[13,42,43]
96HK	96H98K120S	DR3, DR8, DR11, DR12, DR13, DR14	A, H, M	[12,16,23]
$96Y_2$	96Y98E120N 180L181T183P	DR4	A, M	[12,20,35,44]
98Q	96H98Q120S	DR52	A, H, M	[12,45,46]
104A*	104A	DR4, DR7, DR9, DR51, DR52	A, M	[12,13]
108T*	108T	DR51	A, M	[12,47]
$142M_3$	140A142M 133L135G 96Q98K120S	DR15, DR16	A, M	[12,16,18,48]
181M	181M	DR7, DR9, DR10, DR53	A, M, S	[11,12,20]

The subscripted numbers on annotations $48Q_6$, $96Y_2$ and $142M_3$ indicate possible numbers of epitopes shared within the same group of DRB antigens. The DP superscript of $57DE^{DP}$ indicates that this epitope is also found on DP alleles.

[a] Antibody sources and methods are: A, alloserum; E, alloserum eluate; H, human mAb; M, mouse mAb; and S, site mutagenized alleles with residue substitutions.

The 4Q epitope is shared between DRB1 antigens DR7 and DR9 and the DRB4 antigen DR53. Sequence position 4 has also an arginine residue shared between all remaining DRB1 antigens as well as DRB3 and DRB5. Several mouse monoclonal antibodies have verified 4R; this epitope has a provisional status because we have no conclusive data yet about its reactivity with informative human alloantibodies. The 4Q and 4R epitopes constitute a bi-allelic system which is well exposed on the molecular surface.

DR8 and DR12 share the antibody-verified 16Y epitope which is defined by 16Y and the nearby hidden 13G residue. These antigens share also a distinct 70D71R13G configuration but its influence is unknown.

Many antibodies react only with DRB1*07:01 which has $25Q_3$ including an epitope defined by 25Q and 26F. Studies with mutated DRB*07:01 alleles have shown that the Q25R substitution abolishes the reactivity with two DR7-specific mAbs (SFR16-DR7M and TAL13.1), whereas a nearby K14E substitution also affected binding [20]. Moreover, the R25Q substitution on DRB1*04:03 induced reactivity with antibody.

It should be noted that sequence position 25 has also an arginine residue shared between all DRB1 antigens except DR7 as well as DRB3 (DR52) and DRB5 (DR51). Several mAbs are specific for an epitope defined by 25R and the R25Q mutation leads to non-reactivity [20]. The 25R-defined epitope has a high frequency: our experience (unpublished data) has shown that certain DR7-homozygous patients may have 25R-specific antibodies that react with all antigens except DR7 and DR53 which has 25W.

All DRB4 (DR53) alleles have six unique configurations which besides 25W26N include 18L, 40Y41N44L, 48Q, 81Y and 180M in non-overlapping molecular locations. DR53-specific antibodies are quite common and although there is no information which configuration is actually recognized, we use the $48Q_6$ eplet annotation to indicate six possibilities.

In 1987, the serologically defined DR52 specificity was divided with antibodies into three DRB3 subgroups: DR52a (DRB3*01), DR52b (DRB3*02) and DR52c (DRB3*03) [46,49]. Several antibody-verified epitopes are on DR52 molecules: 98Q on all DRB3 (DR52), 51R on DRB3*02:02 (DR52b), 74R on DRB3*01:01 (DR52a) plus DR3 and 77N on all DRB3 (DR52) plus DR3. Mouse mAb 7.3.19.1 is specific for the 77N-defined epitope; the N77T substitution on mutated DRB1*03:01 abolishes reactivity and the T77N substitution on mutated DRB1*11:01 generates reactivity with this mAb [38,39]. Conversely, all DRB antigens except DR3 and DR52 express the antibody-verified 77T-defined epitope.

DR51 (DRB5) has a distinct antibody-verified epitope 108T. It shares with DR1 the immunogenic 96EV epitope; sensitization by DR51 often leads to antibodies that also react with DR1 whereas DR1-induced antibodies often cross-react with DR51 [43].

The 57DE epitope is unique for DRB1*11 alleles (DR11) and has been verified with several antibodies. Many 57DE-specific antibodies also react with a large group of DPB alleles including DPB1*02:01 (but not DPB1*02:02), DP3, DPB1*04:02 (but not DPB1*04:01), DP6, DP9, DP10, DP14, DP16, DP17, DP18 and DP28; all of them carry a structurally similar 55DE eplet. Polymorphic DRB residue 58E and DPB residue 56E play a central role in this DRB–DPB shared epitope; residue substitutions on mutated DRB molecules greatly affect reactivity with informative mAbs [31]. These findings suggest two closely related epitopes induced by a DR11 mismatch. The 57DE eplet is restricted to DR11 and must have another molecular configuration unique on DRB but absent on DP. The other epitope annotated as $57DE^{DP}$ reflects the cross-reactivity between 58E on DRB and 56E on DPB. As noted below, 56E-specific antibodies induced by DPB mismatches can be DP-restricted or cross-reactive with DR11.

The DR4 alleles in the Luminex panel share the antibody-verified $96Y_2$ which is defined by unique polymorphic residues 96Y

Table 3
Current listing of antibody-verified HLA-DQ epitopes.

DQB1 Epitope*provisional	Polymorphic residue descriptions	Epitope-carrying antigens and/or alleles in Luminex kits	Verified with[a]	References
45EV	45E46V47Y	DQ7	A, M, E	[16,51–56]
$45GE_3$	45G46E47F 74A75V77R 52L53L55L56P57A	DQ2	A, M, H, S, E	[16,18,19,55–59]
45GV	45G46V47Y	DQ4, DQ5, DQ6, DQ8, DQ9	A, M, S, E	[51,52,54,56,60–62]
$46VY_3$	46V47Y 28T 52P	DQ3, DQ4, DQ5, DQ6 (nonDQ2)	A, M, E	[3,55,56,63,64]
$52PL_3$	52P53L 140T 182N	DQ3, DQ4	A, M, E	[16,56,63–65]
$52PQ_2$	52P53Q55R56P 84E85V86G90I	DQ5, DQ6	A, M, H, E	[3,16,18,19,55,56,66,67]
52PR	52P55R	DQ4, DQ5, DQ6	A, M, H, E	[3,16,18,19,55,56,68]
55PP	52P53L55P56P	DQ3	A, M, H, E	[3,16,18,19,55,56,69]
$74SR_3$	71A74S77R 116I 125S	DQ5	A , M, E	[3,55,56]
$74SV_2$	74S75V 26G	DQ4, DQ5	A, H	[65,70]
77R*	77R	DQ2, DQ5	A, E	[56]
77T*	77T	DQ3, DQ4, DQ6	A, E	[56]
$84QL_3$	84Q85L86E90T 53L 125A	DQ2, DQ3, DQ4	A, E, M	[3,56,63,71]
125SQ*	125S126Q	DQB1*05:01/03	A, E	[56]
$140A_2$*	140A 182S	DQ2, DQ5, DQ6	A, E	[56]
DQA1 Epitope				
$40GR_3$	40G41R45V 47C48L 50V51L52R53Q54F55R	DQA4, DQA5, DQA6	A, E	[56,63,65,72]
47KHL	47K52H54L	DQA2	A, E	[56,63,65]
$75S_3$	75S76L 163E 175K	DQA5	A, E, H	[68,72]

The subscripted numbers on annotations $45GE_3$, $46VY_2$, etc. indicate possible numbers of epitopes shared within the same group of DQ antigens.
[a] Antibody sources and methods are: A, alloserum; E, alloserum eluate; H, human mAb; M, mouse mAb; and S, site mutagenized alleles with residue substitutions.

Table 4
Current listing of antibody-verified HLA-DP epitopes.

DPB1 Epitope*provisional	Polymorphic residue descriptions	Epitope-carrying alleles in Luminex kits	Defined by[a]	References
35FV	35F36V	DP2, DP3, DPB1*04:02, DP5, DP6, DP8, DP9, DP10, DP14, DP17, DP18, DP19, DP23	A, M	[76–79]
56A*	56A57E	DP1, DPB1*02:02, DPB1*04:01, DP5, DP11, DP13, DP19, DP23	A	[80]
56E	56E	DP1, DPB1*02:01, DP3, DPB1*04:02, DP6,DP9 DP10, DP14, DP16, DP17, DP18, DP28	A, H, M	[23,77,79,81,82]
$56E^{DR11}$	56E or 58E on DR11	DP1, DPB1*02:01, DP3,DPB1*04:02, DP6,DP9 DP10, DP14, DP16, DP17, DP18, DP28 + DR11	A, H, M, S	[22,30–34,77,80,83]
57D	55D56E57D	DP3, DP6, DP9, DP14, DP17	A, M	[77,79,84,85]
$56EE^{DR11}$	55D56E57E or 57D58E59E on DR11	DPB1*02:01, DPB1*04:02, DP8, DP10, DP18, DP28 and DR11	A, M	[22,77,84,85]
84DEAV	84D85E86A87V	DP1, DP3, DP5, DP6, DP9, DP10, DP11, DP13, DP14, DP16, DP17, DP19	A, H, M	[23,65,77–80,84–86)
85GPM	85G86P87M	DP2, DP4, DP15, DP18, DP23, DP28	A, M	[22,77–80,84,87]

The DR11 superscript of $56E^{DR11}$ and $56EE^{DR11}$ indicates that this epitope is also found on DR11.
[a] Antibody sources and methods are: A, alloserum; E, alloserum eluate; H, human mAb; M, mouse mAb; and S, site mutagenized alleles with residue substitutions.

and 182L exposed on the molecular surface; there is also a unique 13H residue in the peptide-binding groove which cannot make direct contact with antibody. Which eplets do DR4-specific antibodies recognize? Mutated DR4 molecules with substitutions L180V and T181M do not react anymore with the DR4-specific mAb (NFLD.D1) and this indicates a critical role of 180LT eplet [20]. Conversely, these mutations do not affect the reactivity with another DR4-specific mAb (GS359-13F10) and this mAb may recognize another eplet unique for DR4 possibly 96Y [50].

The antibody-verified $142M_3$ on DR15 and DR16 reflects three unique polymorphic residues: 140A142M, 133L135G and 96Q98K120S; it is not known which configuration is specifically recognized by DR15 + DR16-specific antibodies.

Table 2 lists six antibody-verified epitopes with provisional status. The 11STS epitope is defined solely by the unique 13S which has nearby polymorphic residues 11S and 12T in the peptide-binding groove, none of them appear accessible for direct contact with antibody. It is possible that they can influence the conformation of nearby monomorphic surface residues such as 14E thereby giving rise to the 11STS epitope. More studies are needed especially those with mutated alleles with informative residue substitutions. A similar conclusion was reached for the human mAb-verified 37YV which is defined by hidden residues 37Y and 38V. The antibody-verified 4R, 70QT and 73A are considered provisional because there are no data with informative alloantibodies or eluates of absorbed allosera. Similarly the provisional status of 104A and 108T reflect incomplete data.

3.2. Antibody-verified HLA-DQ epitopes

Fifteen DQB and three DQA epitopes have been verified so far with specific antibodies (Table 3). They are in sequence positions 45–140. Some antibody-verified epitopes such as 45EV on DQ7, $45GE_3$ on DQ2, 55PP on DQ3, $52PQ_2$ on DQ1 (DQ5 + DQ6), and $74SR_3$ on DQ6 correspond to well-defined serological DQ specificities.

$45GE_3$ may represent three distinct eplets defined by residues 45G46E47F, 52L53L55L56P57A and 74A75V77R on the molecular surface. A triple substitution G45E + E46V + F47Y on mutated DQB1*02:02 led to a drastic reduction in the reactivity with DQ2-specific human and mouse mAbs whereas S30Y, I37Y, A57D, K71T and A74E had no effect. [58,59]. Although these mAbs

apparently recognize an epitope related to 45G46E47F it is possible that other DQ2-specific antibodies react with other epitopes. DQ2 has also unique polymorphic residues 28S, 30S and 37I in antibody-inaccessible positions but they may influence the conformation of nearby surface residues giving rise to distinct epitopes.

$52PQ_2$ on DQ1 represents two separate configurations 52P53Q55R56P and 84E85V85G90I in opposite locations on the top of the DQB molecule. $74SR_3$ on DQ5 represents one 71A74S77R eplet on the top of the molecule and two unique polymorphic residues 116I and 125S in the membrane-proximal domain. There are no reports addressing which configuration is recognized by specific antibodies.

Several antibody-confirmed DQB epitopes are shared between multiple alleles. They are 45GV (on DQ4, DQ5, DQ6, DQ8 and DQ9), $46VY_3$ (on all DQ except DQ2), $52PL_3$ (on DQ3 and DQ4), 52PR (on DQ4, DQ5 and DQ6), $74SV_2$ (on DQ4 and DQ5) and $84QL_3$ (on DQ2, DQ3 and DQ4).

Four antibody-verified DQB epitopes 77R, 77T, 125SQ and 140A have a provisional status. These epitopes were recently reported by El-Awar and co-workers who tested the reactivity of eluates of absorbed sera from transplant patients with a panel of DQ heterodimers on a Luminex platform [56]. Additional studies are needed to confirm the antibody verification of these epitopes.

Table 3 lists only three antibody-verified DQA epitopes: $40GR_3$ (on DQA4, DQA5 and DQA6), 47KHL (on DQA2) and $75S_3$ (on DQA5). Our experience indicates that other DQA (and DQB) epitopes are recognized by antibodies in transplant patients [65] but more detailed documentation is needed.

3.3. Antibody-verified HLA-DP epitopes

Table 4 lists eight antibody-verified DPB epitopes. Except for 35FV, all of them reside in amino acid sequences 55–57 (five epitopes) and 84–87 (two epitopes).

The provisionally antibody-verified 56A epitope is shared between DP1, DPB1*02:02, DPB1*04:01, DP5, DP11, DP13, DP15, DP19 and DP23

Residue 56E plays a critical role in a group of epitopes shared between DP1, DPB1*02:01, DP3, DPB1*04:02, DP6, DP9, DP10, DP14, DP16, DP17, DP18 and DP28 in the Luminex panel. Several studies with human and mouse mAbs as well as informative allosera have shown the antibody verification of the 56E defined epitope on DPB; in Table 4 this epitope is referred to as 56E. DR11 has a unique 58E-defined epitope that can cross-react with the 56E-defined epitope on DPB. Indeed many antibodies have been reported as specific for DR11 plus all 56E-carrying DPB alleles. Moreover, residue substitutions on mutated DR11 and DPB molecules have provided further support of this epitope [31,33,34] which has been referred to as $56E^{DR11}$ to indicate cross-reactivity with DR11. As shown in the previous section, some DR11-induced antibodies react also with the 56E-carrying DPB alleles whereas as others react only with DR11. Thus, the DR11-induced $57DE^{DP}$ is the same epitope as the DPB-induced $56E^{DR11}$.

The 56E-carrying DPB alleles have two residue configurations in positions 55–57, namely DED (on DP3, DP6, DP9, DP14 and DP17) and DEE (on DPB1*02:01, DPB1*04:02, DP8, DP10, DP18 and DP28 and also on DR11). Each configuration represents a distinct antibody-verified epitope, namely 57D and $56EE^{DR11}$. It should be noted that $56E^{DR11}$ and $56EE^{DR11}$ represent two distinct antibody-verified DPB epitopes that cross-react with DR11.

The 84–87 sequence region has two well-documented antibody-verified epitopes: 84DEAV (on DP1, DP3, DP5, DP6, DP9, DP10, DP11, DP13, DP14, DP16, DP17 and DP19) and 85GPM (on DP2, DP4, DP15, DP18, DP23 and DP28).

Although there are several reports about DPA-reactive antibodies in sera from transplant patients [65,73–75], there is at present insufficient documentation which DPA epitopes are specifically verified.

4. Discussion

This is the first report about antibody-verified HLA class II epitopes recorded in the HLA Epitope Registry on the http://www.epregistry.com.br website. The current list of 24 DRB, 18 DQ and 8 DP epitopes is the result of a critical structural analysis of published data by many investigators as well as our own experience with class II specific antibodies.

Needless to say, the current repertoire of antibody-verified epitopes must be considered incomplete but we plan to update the Registry with new data. HLA professionals are invited to submit informative data (including from publications not cited in this report) about HLA antibody reactivity patterns especially if they recognize new and less well documented epitopes. The Registry website has instructions how to submit information about antibody reactivity patterns with HLA panels and the sensitizing event including if possible, HLA types of antibody producer and immunizer. Moreover, additional data would be helpful such as absorption/elution studies with selected alleles and the use of mutated alleles with specific residue substitutions.

Certain antibody-verified epitopes have a preliminary status because they have been solely defined by mouse monoclonal antibodies. They are located in molecular positions that are readily antibody accessible. 4R and 73A are high frequency epitopes and there some preliminary data suggesting that patients who type homozygous for DR7 or DR3, respectively, can make 4R-specific or 73A-specific antibodies that react with virtually all nonself alleles in the panel. However, detailed studies including absorption–elution analyses and testing with mutated alleles are needed for a confirmed status of these epitopes.

So far, all antibody-verified class II epitopes correspond to eplets determined by polymorphic amino acid configurations. We must however, consider the fact that the antibody-combining site has three heavy chain and three light chain Complementarity Determining Regions (CDR) loops that make contact with so-called structural epitopes comprising multiple residues distributed over surface areas of 700–900 square Ångstroms [88–91]. Accordingly, such contact residues must reside on the molecular surface within a radius of about 15 Ångstroms of an eplet [92,93]. The eplet-specific CDR plays a dominant role but other CDRs contacting other residue configurations in the structural epitope participate in the formation of the antibody-epitope complex. Such contact sites can be identified by comparing residue polymorphisms shared between eplet-carrying alleles that specifically react with antibody. Indeed, several antibody-verified HLA class I epitopes correlate with eplets paired with other amino acid configurations [5]. Interestingly, these pairs generally involve self configurations present in the HLA type of the antibody producer [94,95].

Class II epitopes defined by eplet pairs can reside solely on individual α or β chains or they require configurations on both chains. Studies with mutated DRA chains have shown that some antibodies recognize epitopes defined by polymorphic residues on DRB chains paired with residues on monomorphic DRA chains [14]. The Registry does not include epitopes defined by DRB–DRA pairs because they are clinically indistinguishable from epitopes defined solely by polymorphic DRB residues.

On the other hand, there is clinically relevant evidence that certain antibody-verified class II epitopes are unique on DQ-heterodimers rather than the individual DQA or DQB chains [68,72,96–98]. Such epitopes are only expressed by certain DQA–DQB heterodimers. There are also two reports on antibodies recognizing distinct DPA–DPB heterodimers [74,99]. Recently expanded class II

Luminex panels (including combinations of kits from different vendors) will provide opportunities to determine the structural basis of antibody-verified epitopes uniquely expressed on DQ and DP heterodimers.

Although the current repertoire of antibody-verified epitopes is incomplete and more data are needed about potentially clinically relevant epitopes, the HLA Epitope Registry will become a valuable resource for researchers interested in HLA compatibility at the epitope level and investigating antibody responses to HLA mismatches.

Acknowledgments

We thank Mario Sergio Marroquim and Gilberto Coelho for their technical assistance in the development and maintenance of the HLA Epitope Registry Website. We also express our appreciation to Immucor (Gen-Probe, Life Codes) and Thermo Fisher (One Lambda) for their financial support.

References

[1] Duquesnoy RJ, Marrari M, da M. Sousa LCD, de M. Barroso JRP, de SE Aita KM, da Silva AS, do Monte SJH. 16th IHIW: a website for the antibody-defined HLA epitope Registry. Int J Immunogenet 2013;40:54–9.
[2] Radka SF. Monoclonal antibodies to human major histocompatibility complex class II antigens. CRC Crit Rev Immunol 1987;8:23–48.
[3] Marsh SG, Bodmer JG. HLA-DR and -DQ epitopes and monoclonal antibody specificity. Immunol Today 1989;10:305–12.
[4] Barbetti AA, Park MS, Terasaki PI, Aoki J, Geer LI, Clark BD, et al. HLA class II epitope detection by serology. Clin Transpl 1990:533–65.
[5] Duquesnoy RJ, Marrari M, Mulder A, da M. Sousa LCD, Da Silva AS, do Monte SJH. First report on the antibody verification of HLA-ABC epitopes recorded in the HLA Epitope Registry. Tissue Antigens 2014;83(391–400):2014.
[6] Duquesnoy RJ, Marrari M, Mostecki J, da Mata Sousa LCD, do Monte SJH. First report on the antibody verification of MICA epitopes recorded in the HLA epitope registry. Int J Immunogenet 2014;41:370–7.
[7] Duquesnoy RJ, Askar M. HLAMatchmaker: a molecularly based algorithm for histocompatibility determination. V. Eplet matching for HLA-DR, HLA-DQ and HLA-DP. Hum Immunol 2007;68:12–25.
[8] Knowles RW, Flomenberg N, Horibe K, Winchester R, Radka SF, Dupont B, et al. Complexity of the supertypic HLA-DRw53 specificity: two distinct epitopes differentially expressed on one or all of the DR beta-chains depending on the HLA-DR allotype. J Immunol 1986;137:2618–26.
[9] Knowles RW. Structural polymorphism of the HLA class II alpha and beta chains: summary of the 10th workshop 2-D gel analysis. In: Dupont B, editor. Immunobiology of HLA. New York: Springer-Verlag; 1989.
[10] Lardy N, van der Horst A, Van den Berg Loonen E, Bontrop R, de Waal L. Fine specificity of the alloantiserum MSD-51: epitope mapping of HLA-DR53 determinants. Hum Immunol 1991;32:65–71.
[11] Fu XT, Yu WY, Alber C, Benson C, Watts R, Nordwig H, et al. Identification of residues involved in polymorphic antibody binding epitopes on HLA-DR molecules. Hum Immunol 1992;33:47–56.
[12] Cai J, Kohanof S, Terasaki P. HLA-DR antibody epitopes. In: MaT Checka PI, editor. Clinical transplants 2006. Los Angeles, CA: Tearasaki Foundation Laboratory; 2006. p. 103–14.
[13] Cai J, Terasaki PI, Mao Q, Pham T, El-Awar N, Lee JH, et al. Development of nondonor-specific HLA-DR antibodies in allograft recipients is associated with shared epitopes with mismatched donor DR antigens. Am J Transplant 2006;6:2947–54.
[14] Fu X-T, Karr RW. HLA-DRa chain residues located on the outer loops are involved in nonpolymorphic and polymorphic antibody-binding epitopes. Hum Immunol 1994;39:253–60.
[15] Heyes JM, Inoko H, Trowsdale J, Sadler A, Marsh SG, Bodmer J. Fine mapping of eleventh international histocompatibility workshop HLA class II monoclonal antibodies using transfectants. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 – Proceedings of the eleventh international histocompatibility workshop and conference. Oxford: Oxford University Press; 1992. p. 400–4.
[16] Navarrete C, Brown C, De Lange P, Schreuder GMT. 12th international histocompatibility workshop HLA class II monoclonal antibodies study. In: Charron D, editor. HLA genetic diversity of HLA. Functional and medical implication, vol. 1. Paris, France: EDK; 1997. p. 11–7.
[17] Mazzoleni O, Pistillo MP, Falco M, Tazzari PL, Ferrara GB. Characterization of two human monoclonal antibodies recognizing HLA-A30 and HLA-A3 + A31, respectively. Tissue Antigens 1991;38:224–7.
[18] Nelson K, Bodmer J, Martin A, Navarrete C, Strong DM. Micro EIA and monoclonal antibodies. In: Dupont B, editor. Immunobiology of HLA. New York: Springer-Verlag; 1989. p. 292–301.
[19] Kennedy LJ, Marsh SGE, Bodmer J. Cytotoxic monoclonal antibodies. In: Dupont B, editor. Immunobiology of HLA. New York: Springer-Verlag; 1989. p. 301–5.
[20] Fu X-T, Drover S, Marshall WH, Karr RW. HLA-DR residues accessible under the peptide-binding groove contribute to polymorphic antibody epitopes. Hum Immunol 1995;43:243–50.
[21] Ogasawara K, Kasahara M, Nakayama T, Ishikawa N, Kunikane H, Hawkin S, et al. A monoclonal antibody recognizing a polymorphic determinant on HLA-DR antigens except DR7 and DRw9. Tissue Antigens 1985;26:344–7.
[22] Inoko H, Bodmer JG, Heyes JM, Drover S, Trowsdale J, Marshall WH. Joint report on the transfectant/monoclonal antibody component. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 Proceedings of the eleventh international histocompatibility workshop and conference. Oxford, UK: Oxford University Press; 1991. p. 919–30.
[23] Marrari M, Mulder A, Duquesnoy RJ. 2013. Unpublished reactivity patterns of HLA epitope specific antibodies. HLA Epitope Registry (http://www.epregistry.ufpi.br).
[24] Bunce M, Sutton PM, Ting A, Morris PJ. The production of a human monoclonal antibody defining a split of HLA-DRw13 (DRw13b). Tissue Antigens 1990;36:100–2.
[25] Marsh SG, Moses JH, Bodmer JG. HLA class II sequence polymorphism detectable by serology. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 Proceedings 11th international histocompatibility workshop and conference. Oxford, UK: Oxford University Press; 1991. p. 610–9.
[26] Ge J, Bratlie A, Hannestad K. A human hybridoma antibody (TrJ11) recognizing a new HLA-DR epitope shared by DR4, DR8, DR11, and DRB1*1303. Hum Immunol 1995;42:27–36.
[27] Kosinski S, Hammerling U, Yang SY. A human monoclonal antibody to an HLA-DRw53 (MT3)-like epitope on class II antigens. Tissue Antigens 1986;28:150–62.
[28] Fuggle SV, Carter C, Morris PJ. Monoclonal antibody definition of the DRB3 allele, HLA-Dw25. Tissue Antigens 1989;34:149–57.
[29] Berte CC, Gorski J, Reith W, Mach B. Epitope mapping of HLA-DR antigens with the use of DNA-transfected cells. In: Dupont B, editor. Immunobiology of HLA. New York: Springer-Verlag; 1989. p. 245–7.
[30] Pistillo MP, Mazzoleni O, Kun L, Falco M, Tazzari PL, Ferrara GB. Production of two human hybridomas secreting antibodies to HLA-DRw11 and -DRw8 + w12 specificities. Hum Immunol 1991;31:86–93.
[31] Klohe E, Pistillo MP, Ferrara GB, Goeken NE, Greazel NS, Karr RW. Critical role of HLA-DR beta 1 residue 58 in multiple polymorphic epitopes recognized by xenogeneic and allogeneic antibodies. Hum Immunol 1992;35:18–28.
[32] Bodmer J, Bodmer W, Heyes J, So A, Tonks S, Trowsdale J, et al. Identification of HLA-DP polymorphism with DP alpha and DP beta probes and monoclonal antibodies: correlation with primed lymphocyte typing. Proc Natl Acad Sci USA 1987;84:4596–600.
[33] Yu WY, Watts R, Karr RW. Identification of amino acids in HLA-DPw4b and -DR5b1 chains that are involved in antibody binding epitopes using site-directed mutagenesis and DNA-mediated gene transfer. Hum Immunol 1990;27:122–35.
[34] Diaz G, Amicosante M, Jaraquemada D, Butler RH, Gullen MV, Sanchez M, et al. Functional analysis of HLA-DP polymorphism: a crucial role for DPB residues 9, 11, 35, 55, 56, 69 and 84–87 in T cell allorecognition and peptide binding. Int Immunol 2003;15:565–76.
[35] Drover S, Karr RW, Fu XT, Marshall WH. Analysis of monoclonal antibodies specific for unique and shared determinants on HLA-DR4 molecules. Hum Immunol 1994;40:51–60.
[36] Drover S, Marshall W, Karr RW. Contribution of residues 70 and 73 of HLA-DRb1 chains to the binding of monoclonal antibody NFLD.D10. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 Proceedings of the eleventh international histocompatibility workshop and conference. UK: Oxford University Press; 1991. p. 408–10.
[37] Cayrol C, Moro F, Sommer E, Tkaczuk J, Ohayon E, Cambon-Thomsen A. New polymorphic HLA-DR epitopes recognized by three monoclonal antibodies produced against DR103 transfected L cells. Tissue Antigens 1992;40:197–203.
[38] Klohe E, Fu XT, Ballas M, Karr RW. HLA-DR beta chain residues that are predicted to be located in the floor of the peptide-binding groove contribute to antibody-binding epitopes. Hum Immunol 1993;37:51–8.
[39] Ballas M, Eiermann TH, Wolpl A, Goldmann SF. Mapping of an HLA-DRw52-associated determinant on DR beta 1 molecules. Tissue Antigens 1990;36:187–93.
[40] Madrigal JA, Ikeda H, Marsh SG, Heyes JM, Kennedy LJ, Trowsdale J, Bodmer JG. Epitope mapping of an HLA-DR-specific monoclonal antibody produced by using human-mouse transfectant cells. J Immunol 1989;143:4084–9.
[41] Maurer D, Madrigal JA, Gorski J. Thr77 controls a public antibody epitope on DRB1. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 – Proceedings of the eleventh international histocompatibility workshop and conference. Oxford: Oxford University Press; 1992. p. 404–6.
[42] Loh MT, Chan SH, Ren EC. A monoclonal antibody with specificity to the HLA-DR1 and -DR51 antigens. Tissue Antigens 1993;42:100–4.
[43] Marrari M, Duquesnoy R. Why can sensitization by a HLA-DR2 mismatch lead to antibodies that react also with HLA-DR1? Hum Immunol 2009;70:403–9.
[44] Madrigal JA, Belich MP, Benjamin RJ, Little AM, Hildebrand WH, Mann DL, et al. Molecular definition of a polymorphic antigen (LA45) of free HLA-A and -B heavy chains found on the surfaces of activated B and T cells. J Exp Med 1991;174:1085–95.
[45] Kolstad A, Hansen T, Hannestad K. A cytotoxic human-human hybridoma antibody (TrH6) specific for HLA-DRw52. Tissue Antigens 1988;31:90–7.
[46] Taylor CJ, Ugozolli L, Tanigaki N, Tosi G, Bunce M, Ting A, Ferrara GB. Antigen society #29 report (DRw52). In: Dupont B, editor. Immunobiology of HLA. Volume I: Histocompatibility testing, 1987. p. 273–5.

[47] Van den Berg Loonen E, Bignon JD, Du Toit E. AHS#11: DR2 (DR15, DR16), DR15. In: Charron D, editor. HLA proc. twelfth international histocompatibility workshop and conference. Sevres, France: EDK Medical and Scientific International publisher; 1997. p. 91–5.
[48] Bodmer JG, Pickbourne P, Richards S. Histocompatibility testing, 1977.
[49] Fuggle SV, Carter C, Watts F, Kirkley J, Morris PJ. Monoclonal antibody definition of multiple polymorphic epitopes on HLA-DRw52. Hum Immunol 1987;19:255–63.
[50] Maurer D, Gorski J. Transfer of polymorphic monoclonal antibody epitopes to the first and second domains of HLA-DR beta-chains by site-directed mutagenesis. J Immunol 1991;146:621–6.
[51] Schreuder GM, Maeda H, Koning F, D'Amaro J. TA10 and 2B3, two new alleles in the HLA-DQ region recognized by monoclonal antibodies. Hum Immunol 1986;16:127–36.
[52] Kenter MJH, Anholts JDH, Schreuder GMT, Van Eggermond MCJA, Ghyselen GM, Van Rood JJ, et al. Unambiguous typing for HLA-DQ TA10 and 2B3 specificities using specific oligonucleotide probes. Hum Immunol 1989;24:65–73.
[53] Maeda H, Hirata R, Kambayashi H, Koning F, Schreuder GM. Multiple epitopes on a single DQ molecule from the DQw3-carrying haplotypes. Tissue Antigens 1986;28:136–45.
[54] Radka SF, Nelson KA, Johnston JV. HLA-DQw3-related determinants: analysis of subunit and spatial relationships. Hum Immunol 1989;25:225–36.
[55] Deng CT, Cai J, Tarsitani C, El-Awar N, Lachmann N, Ozawa M. HLA class II DQ epitopes. Clin Transplant 2006;2006:115–22.
[56] El-Awar N, Nguyen A, Almeshari K, Alawami M, Alzayer F, Alharbi M, et al. HLA class II DQA and DQB epitopes: recognition of the likely binding sites of HLA-DQ alloantibodies eluted from recombinant HLA-DQ single antigen cell lines. Hum Immunol 2013;74:1141–52.
[57] Ge J, Bartnes K, Hannestad K. A human monoclonal hybridoma antibody (TrJ1) specific for HLA-DQ2. Tissue Antigens 1993;41:81–5.
[58] Viken HD, Paulsen G, Sollid LM, Lundin KE, Tjonnfjord GE, Thorsby E, et al. Characterization of an HLA-DQ2-specific monoclonal antibody. Influence of amino acid substitutions in DQ beta 1*0202. Hum Immunol 1995;42:319–27.
[59] Viken HD, Paulsen G, Drover S, Marshall WH, Sollid LM, Gaudernack G, et al. Influence on antibody recognition of amino acid substitutions in the cleft of HLA-DQ2 molecules. Suggestive evidence of peptide-dependent epitopes. Hum Immunol 1995;44:63–9.
[60] Nordwig H, Kwok WW, Johnson JP. Identification of the amino acid residues contributing to monoclonal antibody-defined DQw1 epitopes. Hum Immunol 1991;31:81–5.
[61] Viken HD, Thorsby E, Gaudernack G. Characterization and epitope mapping of four HLA class II reactive mouse monoclonal antibodies using transfected L cells and human cells transfected with mutants of DQB1*0302. Tissue Antigens 1995;45:250–7.
[62] Petersen JS, Dyrberg T. Production of epitope specific monoclonal IgG antibodies to HLA class II molecules by combining in vivo and in vitro immunization. J Immunol Methods 1992;151:15–26.
[63] Deng CT, El-Awar N, Ozawa M, Cai J, Lachmann N, Terasaki PI, et al. Human leukocyte antigen class II DQ alpha and beta epitopes identified from sera of kidney allograft recipients. Transplantation 2008;86:452–9.
[64] Marrari M, Duquesnoy R. Correlations between Terasaki's HLA class II epitopes and HLAMatchmaker-defined eplets on HLA-DR, -DQ and -DP antigens. Tissue Antigens 2009;74:134–46.
[65] Duquesnoy RJ, Awadalla Y, Lomago J, Jelinek L, Howe J, Zern D, et al. Retransplant candidates have donor-specific antibodies that react with structurally defined HLA-DR, DQ, DP epitopes. Transpl Immunol 2008;18:352–60.
[66] Koning F, Raghoebar J, Schreuder GMT, Schurman R, Bruning H. A monoclonal antibody detecting a DQw1-related determinant. Tissue Antigens 1985;26:100–6.
[67] Dessi V, Sanchez B, Garzon M, Magarino R, Maldonado MD, Nunez-Roldan A. Characterization of three human monoclonal antibodies specific for polymorphic class I and class II HLA antigens. Hum Immunol 1990;27:323–32.
[68] Kolstad A, Johansen B, Hannestad K. Two HLA-DQ-specific human–human hybridoma antibodies (TrG6; TrC5) define epitopes also expressed by a transcomplementing hybrid DQ molecule (DQw7 alpha/DQw4 beta). Hum Immunol 1989;24:15–29.
[69] Viken HD, Thoresen AB, Thorsby E, Hansen T. The cytotoxic HLA-DQ3 reactive human hybridoma antibody 4166 that may distinguish DQ7 + 8 from DQ9. Hum Immunol 1995;42:281–8.
[70] Ge J, Hannestad K. A cytotoxic human hybridoma monoclonal antibody (TrJ6) defining an epitope expressed by HLA-DQ4 and -DQ5. Hum Immunol 1994;39:106–12.
[71] Vitale M, Pistillo MP, Tazzari PL, Falco M, Sun PF, Mantero S, et al. Production and characterization of murine monoclonal antibodies recognizing HLA-DQ polymorphisms obtained by immunizing mice with transfected L cells. Hum Immunol 1992;34:126–34.
[72] Tambur A, Leventhal JR, Friedewald J, Ramon D. The complexity of human leukocyte antigen (HLA)-DQ antibodies and its effect on virtual crossmatching. Transplantation 2010;90:1117–24.
[73] Heyes J, Austin P, Bodmer J, Bodmer W, Madrigal A, Mazzilli MC, et al. Monoclonal antibodies to HLA-DP-transfected mouse L cells. Proc Natl Acad Sci USA 1986;83:3417–21.
[74] Young JA, Lindsay J, Bodmer JG, Trowsdale J. Epitope recognition by a DP alpha chain-specific monoclonal antibody (DP11.1) is influenced by the interaction between the DP alpha chain and its polymorphic DP beta chain partner. Hum Immunol 1988;23:37–44.
[75] El-Awar N, Terasaki M, Cai J, Deng CT, Ozawa M, Lias M, et al. Epitopes of HLA-A, B, C, DR, DQ, DP and MICA antigens. Clin Transpl 2009;2009:295–321.
[76] Marshall WH, Drover S, Mervart H, Younghusband HB, Liu H. Production of a series of monoclonal antibodies to polymorphisms of HLA-DP. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 Proceedings of the eleventh international histocompatibility workshop and conference. Oxford: UK Oxford University Press; 1991. p. 415–7.
[77] Marshall WH, Drover S, Codner D, Gamberg J, Copp MD, Liu HW, et al. HLA-DP epitope typing using monoclonal antibodies. Hum Immunol 1998;59:189–97.
[78] Youngs D. DP alloantibodies. ASHI quarterly 2004:60–2.
[79] Billen EVA, Christiaans MHL, Doxiadis IIN, Voorter CEM, van den Berg-Loonen EM. HLA-DP antibodies before and after renal transplantation. Tissue Antigens 2010;75:278–85.
[80] Cano P, Fernandez-Vina M. Two sequence dimorphisms of DPB1 define the immunodominant serologic epitopes of HLA-DP. Hum Immunol 2009;70:836–43.
[81] Mazzoleni O, Longo A, Angelini G, Colonna M, Tanigaki N, Delfino L, et al. Human monoclonal antibody MP8 detects a supertypic determinant encoded by DPB alleles DPb2.1, DPb3, DPb4.2, DPb8, DPb9, DPb10, and DPb14. Immunogenetics 1989;30:502–5.
[82] Pistillo MP, Karr RW, Klohe E, Mazzoleni O, Ferrara GB. Use of transfectants to identify polymorphic epitopes recognized by human monoclonal antibodies. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991 Proceedings of the eleventh international histocompatibility workshop and conference. Oxford, UK: Oxford University Press; 1991. p. 413–5.
[83] Vaidya S, Hilson B, Sheldon S, Cano P, Fernandez-Vina M. DP reactive antibody in a zero mismatch renal transplant pair. Hum Immunol 2007;68:947–9.
[84] Tongio MM, Van der Berg Loonen E, Bignon JD, Chandanayingyong D, Dormoy A, Eiermann T, et al. HLA-DP detected by serology. In: Charron D, editor. Genetic diversity of HLA functional and medical implication: proceedings of the twelfth international histocompatibility workshop and conference. Paris, France: EDK; 1997. p. 135–8.
[85] Deng C-T, Cai J, Ozawa M, El-Awar N. HLA class II DP epitopes. Clin Transpl 2007:195–202.
[86] Kolstad A, Hannestad K. A supertypic HLA-DP specificity defined by two human–human hybridoma antibodies (TrB50; TrE11). Hum Immunol 1989;25:247–56.
[87] Viken HD, Gaudernack G, Thorsby E. Characterization of a monoclonal antibody recognizing a polymorphic epitope mainly on HLA-DPw2 and DPw4 molecules. Tissue Antigens 1989;34:250–9.
[88] Kabat EA. The structural basis of antibody complementarity. Adv Protein Chem 1978;32:1–75.
[89] Chothia C, Lesk A, Tramontano A, Smith-Gill S, Air G, Sheriff S, et al. Conformation of immunoglobulin hypervariable regions. Nature 1989;342:877–83.
[90] Davies D, Padlan E, Sheriff S. Antibody–antigen complexes. Annu Rev Biochem 1990;59:439–73.
[91] MacCallum RM, Martin ACR, Thornton JM. Antibody–antigen interactions: contact analysis and binding site topography. J Mol Biol 1996;262:732–45.
[92] Duquesnoy RJ. A structurally based approach to determine HLA compatibility at the humoral immune level. Hum Immunol 2006;67:847–62.
[93] McCutcheon JA, Smith KD, Valenzuela A, Aalbers K, Lutz CT. HLA-B*0702 antibody epitopes are affected indirectly by distant antigen residues. Hum Immunol 1993;36:69–75.
[94] Duquesnoy RJ, Mulder A, Askar M, Fernandez-Vina M, Claas FHJ. HLAMatchmaker-based analysis of human monoclonal antibody reactivity demonstrates the importance of an additional contact site for specific recognition of triplet-defined epitopes. Hum Immunol 2005;66:749–61.
[95] Marrari M, Mostecki J, Mulder A, Balazs I, Claas F, Duquesnoy R. Human monoclonal antibody reactivity with HLA class I epitopes defined by pairs of mismatched eplets and self eplets. Transplantation 2010;90:1468–72.
[96] Kwok WW, Thurtle P, Nepom GT. A genetically controlled pairing anomaly between HLA-DQ alpha and HLA-DQ beta chains. J Immunol 1989;143:3598–601.
[97] Barabanova Y, Ramon D, Tambur AR. Antibodies against HLA-DQ alpha-chain and their role in organ transplantation. Hum Immunol 2009;70:410–8.
[98] Tambur A, Rosati J, Roitberg R, Glotz D, Friedewald JJ, Leventhal JR. Epitope analysis of HLA-DQ antigens: what does the antibody see? Transplantation 2014;98:157–66.
[99] Kishi H, Okumura A, Tong J-J, Sugiyama E, Matsuno H, Minowada J, et al. A murine monoclonal antibody (928) recognizing a new epitope formed with a combination of HLA-DPA1*0201 and DPB1*0301 gene products. Hum Immunol 1997;56:114–24.