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Review

Epitope-Level Matching—A Review of the Novel Concept of Eplets in Transplant Histocompatibility

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Abstract: The development of *de novo* donor-specific antibodies is related to the poor matching of the human leukocyte antigen (HLA) between donor and recipient, which leads to dismal clinical outcomes and graft loss. However, new approaches that stratify the risks of long-term graft failure in solid organ transplantation have emerged, changing the paradigm of HLA compatibility. In addition, advances in software development have given rise to a new structurally based algorithm known as HLA Matchmaker, which determines compatibility at the epitope rather than the antigen level. Although this technique still has limitations, plenty of research maintains that this assessment represents a more complete and detailed definition of HLA compatibility. This review summarizes recent aspects of eplet mismatches, highlighting the most recent advances and future research directions.

Keywords: HLA Matchmaker; eplet mismatch; de novo donor-specific antibodies; solid organ transplantation

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1. Introduction

Although there have been many breakthroughs in solid organ transplantation, histocompatibility remains a challenge. Poor HLA matching results in the formation of *de novo* donor-specific antibodies (dnDSA), which in turn lead to worse clinical outcomes and diminished graft survival [1]. Understanding how these antibodies (Abs) are developed can offer strategies to prevent their formation and could significantly improve long-term solid organ transplant results.

Advances in molecular analysis and computational software have given rise to a new concept of eplets, which are defined as clusters of polymorphic amino acids located on the surface of HLA molecules. Eplets have been described as functional epitopes as they include amino acids that can be recognized by anti-HLA antibodies from among the whole amino acid structure that comprises an HLA epitope. This provides a higher resolution view of the antigen–antibody binding and a mechanistic explanation for the old idea of cross-reactive serological groups [2].

Despite the fact that there is still much to elucidate, this new paradigm has started to be the subject of intense research, with great potential for incorporation into clinical practice in the form of thresholds for the number of donor–recipient eplet mismatches (MMs) and as part of the scoring in the organ allocation system.

In this review, we provide an up-to-date summary that is focused on the evaluation of some of the novel research that pioneered this concept, encompassing its application, organ-specific challenges as well as its limitations.

2. The Effects of Poor HLA Matching

Allograft allocation is a complex process. Currently, there are numerous factors such as the urgency of transplant, the lack of donor information, and the type of organ being allocated; because of this, it is often difficult to take HLA matching into account [3].

It is crucial to consider donor–recipient HLA matching because multiple MMs at first transplant results in the reduced lifetime of a functional graft. In the case of renal transplants, DR matching becomes a balance between waiting for dialysis, which increases morbidity and mortality, and accepting a somewhat mismatched donor [4,5]. An illustrative example of the former argument is the initiative called Share35, which grants children top priority in obtaining kidneys from deceased donors (DD) less than 35 years old in order to reduce long waiting times regardless of HLA matching, with the exception of 0 MMs [6].

Taking advantage of the Share35 paradigm, in 2007, Crafter et al. analyzed a Canadian retrospective cohort of 98 patients divided into two eras: before and after Share35 [7]. The requirements were ABO compatibility, negative cross-match, donor age between 5 and 45, but irrespective of HLA matching. This study assessed the impact on the length of time that patients were waitlisted and the quality of organs transplanted, and found that with the new policy, the waiting was ten times shorter than before. In addition, all of the patients were transplanted within six months. These results were then compared to a 25% transplant rate within six months of listing in the pre-Share35 era. Moreover, organs transplanted were also better by all clinical variables assessed [7].

Perhaps given more and more effective immunosuppression protocols, the importance of HLA MMs has diminished over time and does not play that big of a role as it once did in short-term graft survival. With regards to the compromise of time on the waiting list vs. proper HLA matching, we could also add the non-immunological indices of organ quality (i.e., creatinine, level of steatosis). The ideal organ allocation policy would take all three variables into account, and rather than disposing of HLA matching completely, it would be worthwhile to at least match in one locus such as the DR, which has been associated with better outcomes [8].

It has been shown that the risk of kidney graft failure increases with HLA MM in unsensitized recipients [9], with antibody-mediated injury being the main finding in biopsies of chronically rejected kidney allografts [10]. Stressing measures that reduce the humoral alloresponse would improve long-term graft survival. HLA matching is not considered at all in the case of lung transplant (LTx), in contrast to that of kidney, due to the urgency and the fact that there is no replacement therapy. However, it is known that an HLA MM is associated with dnDSA, which is related to chronic humoral rejection or chronic lung allograft dysfunction (CLAD) [11,12].

3. New Concept of Eplets

Our knowledge of the humoral immune response has dramatically increased in the past few years. It has long been recognized that recipient anti-HLA Abs bind to the polymorphic mismatched non-self HLA molecule expressed in the allograft, possibly triggering a graft loss or an unfavorable prognosis. What is novel and important is knowing that this binding is not against the whole antigen structure but rather against specific regions known as epitopes. Duquesnoy and colleagues have developed an algorithm known as HLA Matchmaker, which considers HLA alleles as strings of distinct molecular configurations that can eventually be recognized by antibodies [13].

The HLA Matchmaker software describes antibody-verified epitopes that have the ability to elicit an immune response, i.e., produce specific antibodies [14,15]. It is the polymorphic amino acid tridimensional configuration within the epitope that is referred to as an eplet. In short, for a recipient to develop dnDSA, there has to be an HLA mismatch. However, it has to be accessible at the protein level in its quaternary structure, and this accessibility can be predicted with a stereochemical modeling software [16,17].

In a 2015 pediatric cardiac transplant study, Sullivan et al. evaluated 4851 transplants and focused on the eplet MM loads in donor–recipient pairs. The HLA Matchmaker

software was used to quantify structural differences between donors and recipients in order to evaluate graft loss risk [18]. It has been described that specific allele MMs are more antigenic than others, and some are even inconsequential. The authors stated that more mismatches at the allele level were also correlated with more eplet MMs. They observed that recipients with 10–20 or more class I eplet MMs experienced increased long-term graft loss versus recipients with less than ten eplet MMs in class I, establishing a possible cut-off point of <10 MMs [18]. They explained that even if recipients had 2–4 class I antigen MMs, which are generally considered high-risk, but had less than ten eplet MMs in class I, graft survival was comparable with that of low-risk patients. This suggests that not all HLA MMs are equal; in other words, an allele mismatch is not the same as an eplet mismatch. Thus, the Ab-accessible polymorphic regions (eplets) could be key to a more objective approach in defining the risk of anti-HLA Ab development and chronic allograft rejection [18].

We can see how donor–recipient pairs with a similar number of antigen MMs can vary considerably with eplet MMs, further highlighting the fact that eplet matching presents an exceedingly significant advantage compared with HLA matching. The eplet model offers far greater discrimination power and matching capacity. Thus, even though the two potential recipients have an equal number of HLA MMs, by analyzing it at the eplet level, one can see how one recipient is clearly a better match (See Figure 1). Using eplet matching, we can benefit from data at the molecular level [18]. This may aid in identifying recipients at risk of long-term graft loss and who could also benefit from post-transplant surveillance and management. Other studies have found that eplet MMs are associated with acute rejection in kidney transplant recipients, with 20 or more mismatches being the threshold [19].

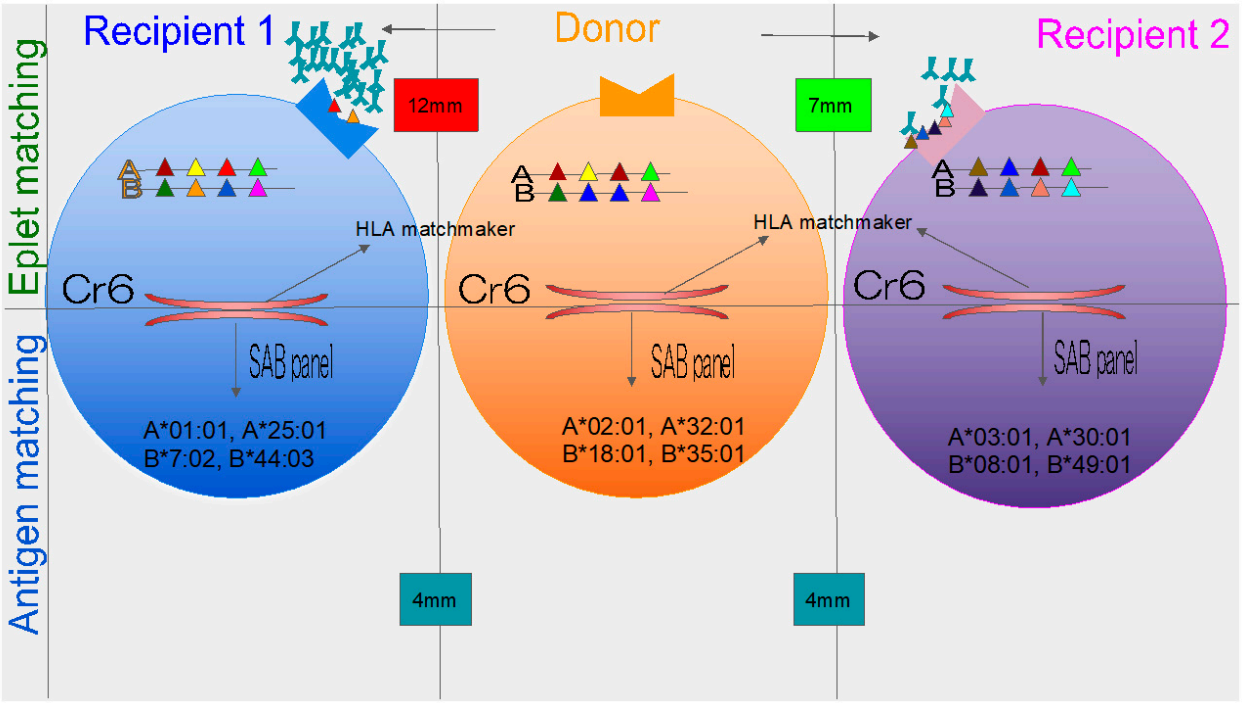

Figure 1. Schematic comparison between antigen and eplet matching approaches. The HLA typing for donors and two potential recipients reveals an equal number of mismatches (mm) at A and B loci. However, eplet matching views antigens (A, B) as a sequence of polymorphic amino acids which adopt a tridimensional conformation in the HLA protein. By considering the quaternary structure, the eplet approach offers far greater discrimination power and matching capacity. Thus, even though the two potential recipients have an equal number of antigen-level mm, recipient 2 is a better match at the eplet level. This could translate into less donor-specific antibody development and better long-term graft survival.

Another similar study, also evaluating the differences between antigen and eplet MM, is the 2016 research by Bryan et al. that evaluated a retrospective cohort of 78 offers for 16 pediatric renal transplant patients to determine the prevalence of DR and DQ mismatching from donor offers during a one-year follow-up [20]. Based on their early age and time of transplant, this is important because a considerable number of children will need to be retransplanted later in life, and performing eplet matching could potentially reduce the development of dnDSA. The authors compared the HLA-matching method with the eplet-matching method, using thresholds established by Wiebe et al. [11]. Using eplet analysis, it was shown that two MMs in the DR antigen corresponded with a 64% risk of developing dnDSA [20]. Thus, this study validates HLA Matchmaker as a tool that has more granularity and as a crucial development that allows for the molecular comparison between donor antigen and self.

The assessment of eplet MM has several drawbacks; firstly, there is a lack of consensus in the cut-off value of eplet MM used in different studies (Table 1). Secondly, a high resolution of HLA type is required to perform proper eplet MM analysis (Table 2 summarizes the differences between antigen and epitope level analysis). The imputational approach for high-resolution HLA typing may render inaccurate results [21].

Table 1. Selected studies and corresponding results of eplet mismatch in solid organ transplantation.

References	Year, Author	Study	Organ	HLA Loci	Observations	Clinical Correlate	Eplet
[11]	2013, Wiebe	p-cohort, n = 286	Renal	DR, DQ	HLA-DR epitope MM load OR = 1.06 * (1.03–1.10) [a] HLA-DQ epitope MM load OR = 1.04 * (1.0–1.02) [a]	dnDSA	-
[19]	2016, Do Nguyen	R-cohort, n = 3499	Renal	All	0–2 HLA MMs + >20 eplet MMs, HR = 1.85 (1.11–3.08) [a]	Risk of rejection	-
[20]	2016, Bryan	R-cochort, n = 16	Renal (peds)	DR, DQ	HLA-DR > 10 MMs, HLA-DQ > 17 MMs	dnDSA	-
[22]	2016, Kaussman	p-cohort, n = 19	Renal (peds)	All	Class I < 10 MMs, class II < 30 MMs	AMR	-
[23]	2015, Wiebe	R-cohort, n = 195	Renal	DR, DQ	HLA-DR > 10 MMs, HLA-DQ > 17 MMs	Synergistic with Tx non-adherence	-
[24]	2017, Lobashevsky	R-cohort, n = 141	Renal	Class I	Threshold > 12 MMs, OR = 9 (1.0–81.2) [a]	AMR, TG, dnDSA, existing DSA	127K
[25]	2021, Tafulo	R-cohort, n = 96	Renal	Class II	Class II eplet MMs, HR = 1.105 (1.011–1.208) [a]	dnDSA	-
[26]	2019, Tafulo	R-cohort, n = 151	Renal	Class II	Class II eplet MMs, HR = 14.839 (1.846–119.282) [a]	AMR	-
[27]	2016, Walton	R-cohort, n = 175	Lung	All	Threshold > 60 eplets MMs	CLAD, ROS	-
[28]	2019, McCaughan	R-cohort, n = 433	Lung	DQ	OR = 4.9	dnDSA	45EV, 45GE3

Table 1. *Cont.*

References	Year, Author	Study	Organ	HLA Loci	Observations	Clinical Correlate	Eplet
[28]	2019, McCaughan	R-cohort, n = 265	Cardiac	DQ	OR = 4.2	dnDSA	45EV, 45GE3
[29]	2020, Osorio-Jaramillo	R-cohort, n = 1167	Cardiac	DR, AB	HLA-DR eplet MMs had inferior 1 year graft survival, HR = 1.14 (1.01–1.28) [a] Risk of rejection: HLA-AB MM load HR = 1.70 (1.29–2.24) [a] and HLA-DR HR = 1.32 (1.09–1.61) [a]	Graft survival and rejection	-
[30]	2019, Nilsson	R-cohort, n = 34,681	Cardiac	DR, DQ	HLA-DR/DQ > 40 eplets MMS HR = 1.11 (1.03–1.21) [a]	Graft loss	-
[18]	2015, Sullivan	R-cohort n = 4851	Cardiac(peds)	All	Class I > 10 MMs	Graft loss	-
[31]	2019, Guiral	R-cohort, n = 43	Liver	C	OR = 3.8 (1.59–8.93) [a]	TCMR	-
[32]	2018, Forner	R-cohort, n = 67	Liver	A	Decreased graft survival, not significant	-	-
[33]	2019, Ekong	R-cohort, n = 42	Liver	DQ	HLA-DQ > 5 MMs	ACR, portal fibrosis score	4Q, 45GE, 52PQ, 52PL
[34]	2018, Kubal	*p*-cohort, n = 80	Liver		Class II MM eplets DRB1,DQA1/B1 was associated with dnDSA OR = 1.2	dnDSA	-

Abbreviations—ACR: acute cellular rejection; AMR: antibody-mediated rejection; CAV: cardiac allograft vasculopathy; CLAD: chronic lung allograft dysfunction rejection; dnDSA: de novo donor-specific antibodies; HR: hazard ratio; MMs: mismatches; OR: odds ratio; *p*-cohort: prospective cohort; Peds: pediatric patients; R-cohort: retrospective cohort; ROS: restrictive obliterans syndrome; TCMR: T cell mediated rejection; Tx: treatment; TG: transplant glomerulopathy. * OR per unit change; [a] 95% confidence intervals.

Table 2. Comparison of antigen-level and epitope-level analyses.

	HLA Antigen Mismatch	Eplet Mismatch
Advantages	1. Ease of measurement 2. Widespread use	1. HLA typing information already available for analysis 2. High-resolution view at molecular level 3. Can guide clinicians to tailor immunosuppression-lowering trials 4. Can help predict patients at risk of long-term graft loss
Disadvantages	1. Lack of granularity 2. Restricts a donor locus without taking into account recipient's whole repertoire of epitopes	1. Needs continued, experimental verification of Ab binding 2. Unclear thresholds and cutoffs

Abbreviations—Ab: antibody.

4. Organs and Eplet

4.1. Mechanism for How dnDSA Are Developed

The development of dnDSA represents the immunologic reaction the donor elicits in the transplant recipient. The Abs that do not preexist but develop after transplantation and are directed against foreign graft HLA are considered dnDSA. The distinction of being

donor-specific is crucial as they are directed against the graft, eventually resulting in the loss of the organ.

In 2016, Kosmoliaptsis et al. devised a numerical approach to determine the immunogenicity of donor HLA [35]. They measured this as the differences in the number of amino acid mismatches and their physicochemical properties, which translate to an amino acid MM score (AMS), an eplet MM score (EpMS), and an electrostatic MM score (EMS), all of which are predictors of DSA in patients listed for retransplant. They found that the assessment of donor HLA immunogenicity based on these methods (AMS, EpMS, or EMS) offered additional information and value to conventional HLA MM grades. Another exciting fact described by the authors was that donor HLA-DR and DQ alloantigens with high AMS, EpMS, or EMS were more prone to developing DSA [35].

Regarding the natural history of dnDSA development, Wiebe et al. proposed a mechanism based on a 2012 prospective six-year follow-up cohort study of 315 patients. They analyzed anti-HLA antibodies pre/post-transplantation and looked for de novo DSA development. They saw that 15% of patients developed post-transplant dnDSA. Their formation began with early inflammatory events, and followed by subclinical injury consisting of peritubular capillaritis, C4d deposition, and glomerulitis. The predictors of dnDSA were the incidence of one or more DRB1 mismatches and nonadherence, with a strong trend toward clinical rejection episodes preceding dnDSA [1].

4.2. Renal

Immune-mediated injury is still the leading cause of renal graft loss despite immunosuppression and modern cross-matching techniques. Moreover, two-thirds of chronically rejected kidney allografts are due to antibody-mediated rejection (AMR) [10,36,37].

Doxiaidis et al. analyzed a retrospective cohort of 456 renal transplant patients in 2007 to evaluate the different effects of HLA-DR matching versus HLA-A and B. They demonstrated that full HLA-DR compatibility was associated with a lower incidence of biopsy-confirmed acute rejection within the first 180 days post-transplant. An additional positive fact described by these researchers was that matching HLA-A and HLA-B was only beneficial if the entire HLA-DR group was compatible, noting that a single HLA-DR incompatibility obliterates the effect of HLA-A and B matching [8].

In the 2016 prospective cohort study by Kaussman et al. [22], a one-year follow-up in pediatric renal transplants utilized the HLA Matchmaker software to develop a kidney allocation strategy using eplet loads. They set eplet thresholds for class I at less than ten and less than 30 for class II. They then compared the development of dnDSA between the exclusion and no-exclusion groups based on the eplet threshold and found that it was a suitable allocation method, with less time spent on the waiting list. It also served as an acceptable MM [38] and dnDSA developed less; however, early clinical outcomes such as AMR were similar between groups [22]. In other words, low levels of dnDSA are associated with better graft survival in the long term despite having similar short-term outcomes concerning AMR.

In 2013, Wiebe et al. performed a retrospective cohort study of 286 renal transplant recipients. They assessed epitope matching and traditional HLA matching as predictors of dnDSA in DR and DQ antigens, as well as the relative immunogenicity of specific epitopes. Once again, HLA Matchmaker was used to characterize epitope MMs, finding that locus-specific MMs were superior in patients who developed HLA-DR and HLA-DQ dnDSA alone [11].

Eplet analysis might serve as a way to identify high-risk patients that will benefit from frequent monitoring post-transplant. The combination of eplet MMs and nonadherence to immunosuppressive medication seems to have a synergistic effect, as Wiebe et al. described in a 2015 retrospective cohort study of 195 participants. They found that a DR load greater than ten eplet MMs and nonadherence had a 35% increased chance of graft loss as compared to 8% if they adhered to their immunosuppression. The threshold was more than 17 eplet MMs for the DQ locus, while for nonadherence, the graft loss was 33% as

compared to 10% [23]. Taken together, these findings suggest that prior to attempting minimization of immunosuppression, providers should consider eplet MM load. Recently, a multicenter study suggested both the assessment of eplet MM and performing a cell-specific assay before kidney transplantation in order to personalize the minimization of immunosuppression with tacrolimus monotherapy [39].

In 2017, Lobashevsky et al. conducted a retrospective study of a cohort of 458 renal transplant recipients, all of whom had low levels of preexisting class I DSA and a mean fluorescence intensity (MFI) of less than 2000; they analyzed the deleterious effects defined by several criteria such as biopsy-proven AMR, transplant glomerulopathy (TG), dnDSA, and increasing MFI of existing DSA. Recipients were divided into two study groups, one with harmful outcomes and the other with expected results. They correlated the patient data and entered them into the HLA Matchmaker software, and saw that the number of MM eplets between DR pairs was a strong predictor of deleterious effects. In this study, the 127K epitope was found to be immunogenic, and when unmatched at this epitope, they observed an odds ratio of 9 for a deleterious effect. They detected a threshold of 12 eplets for MM, with anything higher than this being a strong predictor of a poor outcome [24]. However, to better define the role of eplet MM load in alloresponse, a profound definition of eplet immunogenicity should be provided [40]. Recently, in a sensitization approach after pregnancy, different immunogenic eplet MMs for both class I [14] and class II [15] were identified. The HLA-class II eplet MM in living kidney donors improved the prediction of dnDSA development [25] and AMR [26].

4.3. Lung

Due to the nature, complexity, and urgency of lung transplantation, HLA incompatibility is overlooked. However, the HLA MM in lung transplantation has been associated with chronic allograft lung dysfunction (CLAD) [41]. Matching in lung transplantation is focused on helping to prevent CLAD and its associated morbidity and mortality.

The concept of eplet load is helpful since it allows for the definition of HLA compatibility with greater precision. Although this strategy cannot be used in urgent cases, as has been noted before, knowing the eplet load can guide clinicians in post-transplant monitoring [42]. Tikkanen et al. studied 340 recipients and found that almost half developed dnDSA, and most of them were against DQ, with a hazard ratio of 2.03 for chronic lung allograft vasculopathy. Male sex and ex vivo lung perfusion were independent risk factors in the development of dnDSA [43].

In a 2014 study, Safavi et al. performed a retrospective study of a cohort of 148 patients where they compared the relationship between dnDSA and the development of bronchiolitis obliterans syndrome (BOS), a clinical picture of progressive small-airway obstruction that leads to chronic allograft dysfunction, which is the primary cause of death beyond the first year of a lung transplant. In a multivariate analysis, dnDSA was associated with a significantly higher hazard ratio for BOS at all stages. Other variables related to BOS were female sex and comorbid emphysema [44,45].

Another research that elucidated the possible association of dnDSA development and BOS was conducted by Morrell et al. in a single-center prospective study of 445 participants screening for dnDSA at the two-year follow-up. They detected 13% of dnDSA in the cohort, which presented a significantly reduced disease-free time compared to the group without dnDSA. Using a Cox proportional hazards model, they observed that the development of dnDSA was associated with BOS and high-grade BOS [46].

Not only does eplet matching offer more granularity than antigen/allele mismatches, but it also has a predictive capacity for developing chronic lung allograft dysfunction (CLAD) in the case of lung transplantation [27].

Walton et al. performed a retrospective study of 175 recipients using eplet mismatches to predict CLAD and restrictive obliterative syndrome (ROS). In their sample population, the average eplet load for all classes was 60, thus serving as a threshold for high or low loads. They demonstrated that antigen mismatches correlated with eplet mismatches. The

ability of eplet matching to detect CLAD and ROS was measured, obtaining an area under the ROC curve (AUC) of 0.71 and 0.77, respectively. These findings were significant in utilizing eplet MMs, but not so for HLA MMs [27].

4.4. Cardiac

The donor HLA typing in heart transplantation and the HLA match are limited to potential HLA-sensitized patients on the waiting list, but an HLA-DR mismatch has been associated with early allograft rejection and worse graft survival. Thus, most cardiac transplants are mismatched and result in DSA development, which contributes to the development of cardiac allograft vasculopathy, a multifactorial entity requiring both immune and non-immune factors [12].

In 2011, a retrospective study by Smith et al. analyzed a cohort of 243 patients, measured their HLA antibody status pre- and post-transplant. Most persistent dnDSA were against HLA class II, irrespective of complement fixation and acute rejection stimulus for developing dnDSA [12,47]. Cardiac transplant recipients were HLA-screened before and after transplant. Their goal was to identify persistent dnDSA associated with more immunogenic epitopes and to develop an allocation algorithm that would predict and reduce this occurrence. They identified a risk epitope mismatch (REM) when the donor was DQA1*05/DQB1*02 or DQA1*05/DQB1*03, which generated dnDSA against its mismatched risk epitope of 45EV 45GE3 [48].

In 2020, Osorio-Jaramillo et al. evaluated the association of eplet MMs with post-transplant graft survival, rejection, and cardiac allograft vasculopathy (CAV) in a retrospective study of 1167 cardiac transplanted patients. They determined the number of amino acid differences in Ab-verified HLA eplets between donor and recipient, and showed that high HLA-DR eplet MMs were associated with less graft survival at one year, whereas an eplet mismatch in HLA-A and B had no impact. In addition, high loads of HLA-A, -B, and -DR, the MMs increased the risk of rejection. Finally, they did not find any impact on CAV development. The molecular-level HLA MMs are associated with rejection and worsened graft survival in heart transplant recipients [29].

On the contrary, Nilsson et al. carried out a novel study using the HLA Matchmaker algorithm to stratify risk in a large cohort of heart transplant recipients; their results showed an increased graft loss with the HLA-DR/DQ eplet MM level, but were not superior to HLA-DR/DQ antigen-level MMs [30].

4.5. Liver

The effect of eplet mismatch in liver transplantation has not been studied in detail, and the impact of HLA matching on outcomes remains controversial [49]. For this reason, in 2019, Guiral et al. analyzed eplet MMs in a retrospective study of 43 liver transplant recipients. Patients with a high eplet load in the C locus had higher T-cell mediated rejection [31].

A similar study on liver eplet mismatch conducted by Forner et al. retrospectively analyzed a cohort of 67 recipients for eplet mismatch and found that high eplet loads at the A locus were associated with decreased graft survival, but did not reach statistical significance, and no other loci were found to be predictive [32].

In 2019, Ekong et al. performed a retrospective study of 42 liver recipients. They used HLA Matchmaker to predict the risk of developing Abs and found that 48% developed dnDSA, using >5 MMs as the DQ thresholds. In this cohort, DQB1*02 was associated with acute rejection and a higher portal fibrosis score; additionally, they highlighted the immunodominant epitopes, which were 4Q, 45GE, 52PQ, 52PL [33].

Moreover, in 2018, Kubal et al. analyzed a prospective cohort of 80 liver transplant recipients. They hypothesized that HLA eplet mismatches are a possible marker of immunogenicity and a risk factor for de novo DSA, resulting in 34% of the patients developing only dnDSA class II. They did not find any association between dnDSA formation and acute cellular rejection (ACR) or antibody-mediated rejection (AMR) [34].

Taken together, it remains unclear which HLA locus mismatch is more immunogenic in liver transplants. The data seems to point to class II, as is the case with other solid organs. Though an epitope-matching-based allocation system is not practical for the liver, it can be used to stratify patients according to risk. As is the case for recipients of other organs, higher-risk patients warrant closer surveillance, and lower-risk patients can be placed on tolerance protocols for immunosuppression. This is especially apt in the case of the liver due to its particularities, being one of the most tolerogenic organs transplanted [50].

5. Conclusions

This review summarizes the current evidence regarding the clinical utility of eplet load and epitope-level matching. We have described how donor-recipient pairs with the same number of mismatched alleles can vary considerably depending on the specific protein structure. The nature of the eplets allows for a high-resolution view of the molecular structure and the string of epitopes that comprise the HLA antigen protein.

Consideration of the HLA status at this level can serve clinicians in the transplant field in many ways. Even if it is not part of organ allocation, it can serve as a way for physicians to identify patients at high risk of rejection phenomena and thus adapt their immunosuppression, which is associated with multiple collateral effects such as an increased risk of malignancy and a lower quality of life. If taken into account prior to transplant, a shift towards eplet-level matching—considering risk-epitope mismatches instead of broad antigen—can lead to better outcomes and decrease the likelihood of dnDSA formation, and thus graft survival. It can also help alleviate organ shortage as more donor offers are considered because despite antigen incompatibility, there are no immunogenic eplets in that given locus. It can also grant recipients with exotic HLA types, or those with high-panel reactive antibodies, access to transplant by being selective and not restricting donors with a whole locus.

Many aspects of this new concept remain to be elucidated, such as the thresholds for high and low eplet loads and their respective diagnostic accuracies. Most notable is the immunogenicity of mismatched eplets. Identifying immunogenic eplets would help to identify those patients at risk of de novo antibody development and graft loss. Furthermore, a high-resolution HLA typing for both donor and patients in order to assign eplet MMs should be performed to avoid the potential bias of the imputation HLA antigens [21].

Nevertheless, the move towards a higher resolution and more complex, granular analysis are inevitable. As laboratory techniques and molecular tools have improved, eplets have emerged as another layer of complexity built upon previous concepts. The question is whether this approach should be incorporated into clinical practice, and the fact is that this procedure has progressed from being a purely theoretical exercise to being applied in transplant centers worldwide with promising results.

More data will continue to accumulate on the immunogenicity of each eplet and on the appropriate thresholds that determine high risk. This method must be analyzed in a new way that will ensure graft survival and improved outcomes in transplantation.

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