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REVIEW

HLA and lung transplantation

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Abstract **Lung transplantation is increasingly practiced for patients with end-stage lung disease. The successful outcome of solid organ transplantation today is severely impeded by the production of alloantibodies, mainly directed against the protein products of the HLA complex of the organ donor. While the association between antibody mediated rejection and allograft damage has been well established in renal and heart transplantation, it has not yet been well characterized in lung transplantation. This review addresses the question of HLA matching in lung transplantation and current knowledge of the allogenicity of different HLA class I and II antigens. The role of the antibody mediated immune response is discussed as well as the importance of pre-transplant or *de novo* post-transplant circulating antibodies. Finally, potential mechanisms, which may act individually or in combination, of antibody mediated damage to solid organ transplants are considered.**

Keywords human leukocyte antigen class I and II; lung transplantation; mismatch; obliterans bronchiolitis; alloantibody; antibody mediated rejection

Introduction

Lung transplantation has been developed as an accepted treatment of advanced stage lung disease and more than 50 000 lung transplants have been performed worldwide since the early 1990s. In the International Society for Heart and Lung Transplantation (ISHLT) registry report of 2014, survival at three months was 88%, decreased to 80% after one year, to 65% after three years, to 53% after five years and was 32% after ten years. The recipients who survived to one year post-transplant had a conditional median survival of almost eight years [1]. Survival of patients who have undergone lung transplantation is therefore significantly worse than after other solid organ transplants. For comparison, the 5-year survival after deceased-donor kidney transplantation was 85% in the latest Scientific Registry of Transplant Recipients (SRTR) Annual Report, and the five-year survival after heart transplantation was 75% [2].

A major clinical risk of lung transplantation is rejection. Immunological mechanisms include both cellular and antibody mediated or humoral rejection (AMR). Whereas the complex process of AMR has been intensely studied in renal and heart transplants this is less the case in lung transplantation. The diagnostic criteria for AMR have not yet reached a consensus but were revised in 2016 to include the presence of antibodies, anti-HLA donor-specific-antibodies and characteristic lung histology with or without evidence of complement 4d (C4d) deposition within the graft [3]. Acute cellular rejection (ACR) can be defined as perivascular or peribronchiolar lymphocytic infiltrates without evidence for infection [4].

The underlying mechanisms of both ACR and AMR are due to the immunogenetic disparities between the host and the graft, in which the HLA (human leucocyte antigen) complex plays a pivotal role. In this review we will discuss the HLA profile in lung transplantation, and HLA directed antibodies in organ transplant rejection.

Role of HLA compatibility in lung transplantation

The HLA gene complex is located on chromosome 6, is the most polymorphic gene locus in humans [5], and the molecular products play a major role in immunological responses. HLAs are expressed on almost all nucleated cells, and are the major molecules responsible for graft

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rejection. There are three polymorphic classical HLA class I loci: HLA-A, -B, and -C, and five HLA class II loci: HLA-DRβ, -DQα and β, -DPα and β. In June 2017, 17 166 HLA alleles had been identified (12 544 class I alleles and 4622 class II alleles) [6].

The extensive polymorphism of the HLA gene products is the greatest challenge in matching unrelated donors and recipients in allo-transplantation. The most commonly used HLA typing in organ transplantation worldwide is based on HLA-A, -B, -C and -DR genes. Rapid technological advances have resulted in the development of molecular biology based assays becoming the method of choice.

HLA-A, -B and -DR combined mismatches

First, due to the importance of all four loci in graft-recipient matching and patient survival after lung transplantation, and secondly, because of the strong linkage disequilibrium of HLA antigen transmission (haplotype), many studies have analyzed the effect of their combined mismatches. An early study of Wiser showed that the combined sum of mismatches at the A, B, C, and DR loci had a similar effect on survival for zero to four, versus five to eight mismatches. Graft survival was estimated as 83% versus 62%, and 58% versus 29% at 12 and 36 months, respectively [7].

In 2003, the Eurotransplant Foundation analyzed 590 consecutive patients with first cadaveric lung transplants performed between January 1997 and December 1999. Patient survival was higher for graft recipients with less than or equal to four HLA mismatches compared with more than four mismatches at one year. In this study, when the analysis was stratified by HLA-A, HLA-B or HLA-DR mismatches separately, no difference was noted in the one year survival. However, when all patients were divided into 2 groups of less than four mismatches versus greater than 4 mismatches of merged HLA-A, -B and -DR loci, there was a significant difference in patient survival after one year [8]. Because lung transplantation is often performed in an emergency setting, the authors did not believe that HLA matching would be considered an allocation factor in Eurotransplant, but that posterior HLA typing would nonetheless be necessary, because more than 4 mismatches could be considered as an indicator of patient survival in the long term.

This was confirmed by a retrospective analysis on 3549 lung transplants from UNOS/ISHLT (United Network for Organ Sharing/International Society for Heart and Lung Transplantation) which demonstrated a clear difference in patient survival when transplants were stratified according to the total number of mismatches of HLA-A, HLA-B and HLA-DR ($P = 0.0008$). The results led to the suggestion that the combined number of HLA mismatches was predictive of three- and five-year survival [9].

Wong *et al*. suggested that the decrease in nonspecific alloreactivity in HLA matched patients may be important for the increased risk of post-transplant lymphoproliferative disease (PTLD) in a cohort of Epstein Barr Virus (EBV) seronegative lung transplant patients with donor organs from EBV seropositive individuals [10]. But the analysis of Bakker (2005) on 233 lung transplants did not report a significant increase in the risk of PTLD when patients with more than 4 mismatches were compared with patients with less than or equal to 4 mismatches on HLA-A, -B and -DR loci [11]. However, they proposed a larger cohort study with stratification of each HLA locus separately, because of the different roles of HLA class I and class II in regulating immune responses.

A large-scale study later examined lung allograft survival in relation to the combined number of HLA-A, -B and -DR mismatches in 8020 transplant patients. Decreased graft survival was significantly associated with the number of HLA mismatches (one to six) during the first five years after transplantation. An analysis of patient survival after one year demonstrated the benefit of only 1 mismatch (75%) compared with 4 (69%), 5 (68%) and 6 (67%) mismatches. Survival with 2 (76%) or 3 (74%) mismatches was similar to that with only 1. However, after two years the differences were more marked with 1 (65%), 2 (63%), 3 (59%), 4 (57%), 5 (55%) and 6 (54%) mismatches. After five years the benefit of 1 mismatch (35%) on survival was significantly different from that of patients with 6 mismatches (25%). The conclusion of this study was that compatibility of at least these three HLA loci could strongly protect against immunological rejection [12].

A recent study of 23 538 lung transplantations was designed to assess the effect of total HLA mismatching (HLA-A, -B and -DR) in patient survival. Cox multivariate proportional hazards analysis was used, more than a total of 3 HLA mismatches was associated with a significant increase in the mortality hazard rate (HR 1.214; 95% CI 1.073, 1.374; $P = 0.002$) [13]. Comparison of the group with 3 or more, with the group with 2 or less mismatches revealed an elevated frequency of idiopathic pulmonary fibrosis in the former group, and a greater frequency of chronic obstructive pulmonary disease latter group. However this study was limited by age and body-mass index differences between the groups [13].

Concerning the relationship between the total number of HLA mismatches and bronchiolitis obliterans syndrome (BOS), the most common phenotype of long-term morbidity and mortality in lung transplant recipients development after lung transplantation, an analysis of 16 959 adult recipients from UNOS was performed. Only 18 of 16 959 first-time recipients (0.11%), had 0 mismatches whereas 637 (3.76%) had 2 or fewer

mismatches. Because patients who did not have HLA mismatches were rare, groups with 1 or less mismatches were compared to 2 mismatches at each specific locus. There were 8529 patients (50.3%) with 2 mismatches at the A locus; 11 926 patients (70.3%) with 2 mismatches at the B locus; and 9167 patients (54.0%) with 2 mismatches at the DR locus. These results confirmed the association between the number of HLA mismatches and the risk of BOS after LTx. Univariate Cox proportional hazards analysis found that a 1-unit increase in total HLA mismatch level was significantly associated with a 7.7% greater risk of developing BOS [14].

HLA-A locus and mismatch

One of the first descriptions of the relationship between the outcome of heart-lung transplantation and HLA matching, dates from 1987 in a study of 40 consecutive patients. The patients with zero to one mismatch in the HLA-A locus (n = 10) had less BOS, less severe BOS, and less mortality from BOS than patients with two mismatches in HLA locus A (n = 15). This limited study suggested that the HLA-A locus match may have a long-term benefit and that BOS may be at least partly a result of chronic rejection [15].

In a larger study (n = 112 lung transplantations), Sundaresan reported that the development of BOS was significantly greater for 1 or 2 HLA-A mismatches, in comparison with 0 mismatches [16]. A further analysis of 182 recipients revealed that when patients with 0 or 1 were compared with those with 2 HLA-A mismatches, a benefit to graft survival was noted by univariate analysis. In addition, longer survival was revealed in a multivariate analysis (HR 1.97, 95% CI 1.15 to 3.17, P = 0.013) as well as a lower incidence of BOS in patients with zero or one HLA-A versus 2 mismatches (HR 1.75, 95% CI 1.07 to 2.72, P = 0.03). Following this observation, an analysis of the impact of HLA-A mismatches on both survival and a diagnosis of BOS post-transplant was carried out. The results showed that the negative impact of mismatches increased progressively, as well as the risk of death, with time. However, significant differences were not observed in graft survival when other loci (HLA-B and HLA-DR) were compared in patients with zero or one to those with two mismatches [17].

In Quantz's analysis on 3549 lung transplantations, a number of mismatches at the HLA-A locus associated with lessened one year survival while HLA matching at the B and DR loci did not appear to influence survival in a univariate analysis. An association between mismatching at the HLA-A locus and hospitalization for acute rejection was observed but was not reproduced regarding mismatches at the HLA-B or HLA-DR loci and hospitalization for acute rejection [9].

A systematic analysis of HLA mismatching at each locus (HLA-A, -B and -DR) which included 9791 patients recorded during a ten-year period strongly suggested the negative impact of HLA-A mismatches on BOS development and death [18]. Another study focused on patients with BOS 4 years post-transplantation confirmed the correlation between HLA-A mismatching and the severity of BOS [19]. Hayes *et al*. stratified 16 959 lung transplant recipients from the UNOS database and analyzed the effect of HLA mismatches on BOS development. Competing-risks regression analysis also confirmed a strong association between HLA-A locus mismatches and an increased risk of BOS [14]

A five year study of lung transplant survival showed a significant difference between 0 versus 1, and 1 versus 2 HLA-A mismatches ($P < 0.002$) [12]. In a later study, HLA-A mismatches of 20 279 patients divided into 2 groups were compared, HLA-A mismatches of more than 1 (n = 10 143) were compared with 0–1 (n = 10 136) and the invariant Cox models identified a higher mortality risk associated with a higher number of HLA-A mismatches, as well as an elevated hazard risk of death [13].

HLA-B locus and mismatch

The HLA-B locus is the most polymorphic of the class I genes encoded within the HLA complex. In June 2017, 4828 alleles had been identified [6]. Wisser reported an analysis of 78 lung transplantations in 1996 in which donor and recipient HLA typing was available and the follow-up ranged from one day to over 60 months. This study demonstrated that graft survival was significantly better with one mismatch at the B locus compared with two (67% versus 51% and 61% versus 25% graft survival) at 12 and 36 months, respectively. For the HLA-B and -DR loci combined, a marked matching effect was also observed for zero to two mismatches, versus three to four mismatches (81% versus 62% and 51% versus 29% graft survival at 12 and 36 months, respectively). They therefore concluded that the most significant effect was associated with the B locus [7]. Schulman *et al*. reported that recipients with one or more HLA-B locus matches had a lower cumulative rate of grade A2 or A3 rejections in the 12 months after transplant than recipients with no matches at the HLA-B locus (0 – 1 versus 2 mismatches, 0.59 versus 1.30) [20].

In an analysis of patients hospitalized for rejection and with anti-rejection medication, the degree of mismatching at the HLA-B locus was associated (P = 0.034), this was not the case for mismatches at the HLA-A and HLA-DR loci [9].

Moreover, a correlation between HLA-B mismatches and the stage of BOS, was also reported in 64 recipients, four years post-transplant, and was strengthened by taking into account both HLA-B and HLA-A mismatches [19].

Finally, an analysis of 20 275 lung recipients for HLA-B and survival (more than one mismatch: n = 14 185; one or

less mismatches: $n = 6090$) identified a negative association with patient survival and development of bronchopulmonary sequestration [13,14].

HLA-DR locus

Regarding HLA-DR, Iwaki *et al*. reported the benefit of HLA-DR matching on short-term graft survival (between three and six months) in 74 recipients of lung transplants [21]. Because high-grade acute rejections (pathologic grade A2 or A3) in recipients of lung allografts are a known risk factor for the development of obliterative bronchiolitis, the team of Schulman analyzed 152 recipients and observed that the single significant predictor of early high-grade rejection was that of one or more HLA-DR mismatches. Moreover recipients with one or more matches at the HLA-DR locus had a lesser rate of grade A2 or A3 rejections in the first year compared with non-HLA-DR matched recipients (*P* value 0.73 versus 1.32) [20].

A retrospective study of a cohort of 242 lung transplant patients demonstrated that a shorter survival time because of BOS development or graft loss, was observed for HLA-DR-mismatched recipients. Data from the combined, center-stratified outcome showed a clear difference for recipients with 2 HLA-DR vs. 0 or 1 mismatches. The results of transplantation were most successful in HLA-DR matched recipients, intermediate for those with 1 mismatch and poorest for those with 2 mismatches [22]

An analysis of 12 556 primary lung transplants carried out since the implementation of the Lung Allocation Score (which provides an estimate of patient survival post-transplant) revealed that comparison of one or less versus 2 mismatches was associated with a significant difference in graft survival for HLA-A ($P = 0.042$), for HLA-DR ($P = 0.003$), but not for HLA-B ($P = 0.303$) [23]. Hayes *et al.* analyzed HLA-DR mismatches in 20 137 patients (mismatch > 1: $N = 10\,892$; mismatch 0–1: $N = 9245$). Not only did the univariate Cox models identify an increased mortality hazard rate for a higher number of HLA-DR mismatches (HR 1.057; 95% CI 1.017 to 1.099; $P = 0.005$), but the multivariate Cox models also revealed an elevated hazard death rate for HLA-DR mismatches (HR 1.053; 95% CI 1.007 to 1.101; $P = 0.024$) [13].

Other HLA loci (HLA-C, HLA-DQ)

In a study of heart transplantation, HLA matching at the C or the DQ locus failed to confer improvement in terms of graft survival [24]. No similar study has been carried out in lung transplantation.

A summary of the mismatches of HLA loci in relation to the clinical outcome after lung transplantation is shown in Table 1.

Table 1 Effect of HLA mismatch (MM) on clinical outcome after lung transplantation

HLA loci	Clinical outcome	References
HLA-A, -B and -DR	Poor patient survival	[8,9,12,13]
MM⩾4	Poor graft survival	[7]
	Idiopathic pulmonary fibrosis	[13]
	Obliterans bronchiolitis	[13,14]
HLA-A	Obliterans bronchiolitis	[15,16,18]
MM⩾1	Poor graft survival	[17]
	Poor patient survival	[9,12,18,19]
HLA-B	Poor graft survival	[7]
MM⩾1	Obliterans bronchiolitis	[17,19]
	Bronchopulmonary sequestration	[13,14]
	Acute rejection	[9,20]
HLA-DR	Obliterans bronchiolitis	[20]
MM⩾1	Poor graft survival	[21–23]
	Poor patient survival	[13]
Other loci (HLA-C, HLA-DQ) MM⩾1	Poor graft survival	[24]

Alloantibodies in lung transplantation

The onset of lung transplantation potentially triggers the allogeneic response between host and graft which can occur through both direct and indirect pathways of antigen presentation [25]. The direct pathway depends upon recognition of donor MHC cell surface molecules through antigen presenting cells (APC) and T lymphocyte interactions. The indirect pathway relies upon presentation of processed donor antigen by recipient APC to recipient T cells [26]. The direct pathway is believed to be more relevant for acute allograft rejection while the indirect pathway plays a dominant role in chronic rejection [27,28].

The humoral response due to development of alloantibodies directed against donor HLA antigens (or DSA) is considered as a major cause of allograft damage and loss today in both renal and heart transplantation. Moreover, interaction between the humoral and cellular allogeneic responses has been reported in experimental models of organ transplantation [29].

An obstacle to evaluating the role of DSA in lung transplant recipients is the lack of a distinct set of histologic markers of AMR. DeNicola *et al*. therefore examined the pathologic characteristics of lung transplant biopsies in patients with or without DSA. It had previously been suggested that pulmonary capillaritis is the histological marker of AMR in the lung. Both microvascular inflammation (assessed by neutrophil infiltration) and/or diffuse alveolar damage were examined. Both were more common in patients with DSA, and the combination of DSA and histopathology arousing suspicion of AMR, was associated with development of BOS and mortality. Interestingly, neither C4d nor C3d positivity was more

frequent in biopsies from patients with DSAs [30].

Strong support for the important role of DSA in lung allograft damage comes from a recent demonstration of *in situ* binding of DSA within biopsies from lung transplants. This study is particularly important as it reveals that DSA targets are expressed intragraft, the DSA are of significantly high affinity to require elution and that allograft-bound DSA constitute a risk factor for graft loss in both univariate and multivariate analysis [31].

Pre-existing HLA antibodies characterization

Pre-existing HLA antibodies in patients waiting for transplants are associated with rejection and graft dysfunction after solid-organ transplantation. The allorecognition of pre-existing HLA antibodies directed against the graft could lead to hyperacute rejection within minutes or hours of transplantation. Binding of pre-formed antibodies to HLA antigens expressed by the graft and the subsequent activation of the complement cascade leading to formation of the membrane attack complex has been associated with endothelial cell injury [32] (Fig. 1).

Results from the Organ Procurement and Transplantation Network showed that 18.7% of renal transplant recipients had panel reactive antibodies (PRA) pre-transplant [33]. Lau *et al.* reported that 9% of patients had PRA in 200 lung transplants performed at Duke University Medical Center [34], and that patients with PRA had more BOS and lessened survival two years post-transplantation. In the analysis of 10 237 lung transplant recipients from the UNOS database, the proportion of patients with PRA was 17%. PRA positivity was 1% to 10% in 1259 (72%), 11% to 25% in 249 (14%), and more than 25% in 240 (14%). Increased PRA was associated with increased 30-day and overall mortality [35]. Mangi *et al.* reported that the prevalence of acute rejection at any time was related with recipient class II PRA exceeding 10%. HLA mismatch at the DR locus was associated with acute rejection within two months ($P = 0.0006$) while at four years after transplantation and beyond, it was associated with B locus HLA mismatches [36].

HLA antibodies are observed in 5% to 10% of patients awaiting lung transplant and indicate humoral sensitization to HLA-A, -B, and -DR antigens. Reasons why HLA antibody may develop include prior blood transfusion, pregnancies, connective tissue diseases, or rejection of previously transplanted organs [37].

It is widely considered that hyperacute humoral rejection after lung transplantation stems from direct antibody injury to the lung allograft resulting in intergraft recruitment of innate immune cells. This acute and severe pathology is characterized by infiltration of the alveolar septae by neutrophils, fibrinoid necrosis, and hemorrhagic infarction [38–41]. However hyperacute humoral rejection has become extremely rare because of the implementation of improved screening methodologies for HLA antibodies before transplantation. The degree of pre-transplant sensitization can be indicated by detection of class I or class II HLA antibodies in single-antigen luminex based assays, or in functional cytotoxicity tests (cross-match tests). Results of such analysis can then be correlated to the clinical outcome.

Antibody detection methods

Discussion of donor-specific-antibodies is rendered more

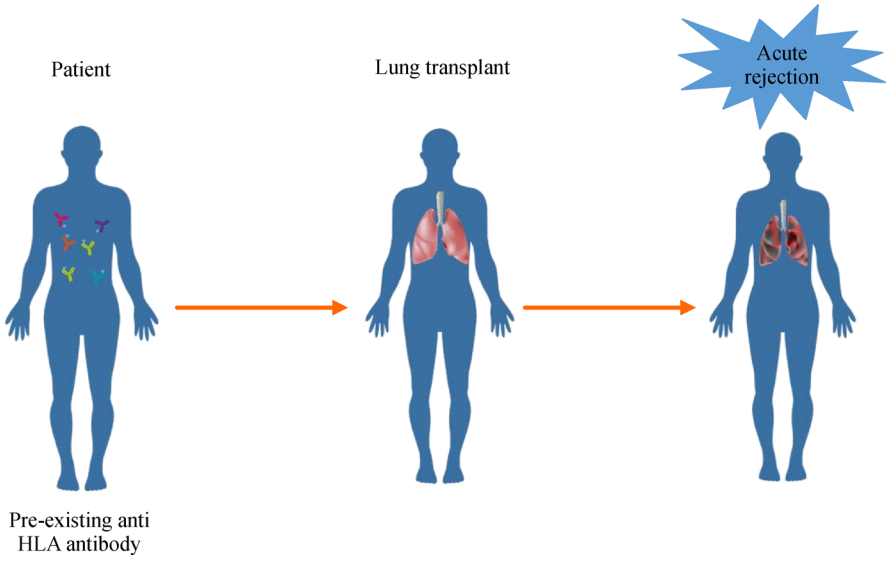

Fig. 1 Presence of pre-existing anti HLA antibodies is a key factor in acute rejection after lung transplantation. The analysis of pre-existing anti-HLA antibodies is mandatory before lung transplantation.

complex because of the use of different testing methods (summarized in Table 2). This problem has been as least partially resolved since all major DSA testing centers now use multiplexed single antigen assays in which recombinant individual HLA glycoproteins are adhered to beads. Patient serum is allowed to react with the glycoprotein-coated beads and antibody binding is detected using a goat-anti-human IgG coupled with a fluorochrome. Fluorescence of each bead is detected by a plate-reader on a Luminex platform and the reactivity with individual HLA antigens coated on the bead is expressed as the mean intensity of fluorescence (MFI). To date, MFIs are standardized within but not between testing centers so comparison of MFIs between centers is not yet a valid procedure. The assay can be modified to include detection of complement binding antibodies [42,43].

Table 2 Testing methods of HLA antibodies in lung transplantation

Methods	Cross-match	Screening	Sensitivity	Comment
CDC	Yes	Yes	+	Requires donor cells
FC	Yes	Yes	++	Requires donor cells
ELISA	No	Yes	++	Can be generic and specific
LUM	No	Yes	+++/++	Can be generic and phenotypic
LUM SAB	No	Yes	+++	Comprehensive allele specification
PRA	No	Yes	++	Generic test only

CDC, complement dependent lymphocytotoxicity. PRA, panel reactive antibody. PRA represents the proportion of the population to which the person being tested will react via pre-existing HLA antibodies. Solid phase immunoassay commercial kits use solubilized HLA molecules bound to a solid matrix. According to the different matrixes and techniques, methods can rely on either enzyme-linked immunosorbent assay (ELISA), conventional flow cytometry (FC) or small footprint lumineux-based fluoroanalyzer (LUM). Single-antigen beads (SABs) are coated with a molecule representing a single cloned allelic HLA-I or HLA-II antigen.

However, it has also been reported that titration of sera before single-antigen based testing more precisely reveals the level of DSA than using the MFI value obtained with undiluted sera [44]. The antibody is tested after dilution and the titer represents the dilution at which a positively binding antibody becomes negative.

Studies of PRAs have been reported. The PRA score is based upon the proportion of the panel of donors to which the patient being tested will react because of existing serum alloantibodies and is expressed as a percentage in a range of 0 – 99%. PRA assays can also be performed using beads coated with a mixture of HLA glycoproteins. Today PRA assays are less common than single antigen assays.

A cellular-based approach to alloantibody detection is used in flow cytometry cross-match assays. Patient serum is allowed to react with donor mononuclear cells, the cells are washed and antibody binding is detected by flow cytometry after addition of a fluorescently labeled anti-human IgG. Antibody reactivity is expressed as the mean fluorescence channel shift over the background value. Another cross match assay depends on complement-dependent cytotoxicity after antibody binding to donor mononuclear cells.

The availability of molecular biology based HLA-typing of donors has led to the development of virtual cross-match assays. The accuracy of this approach relies upon a comprehensive initial HLA-typing.

In lung transplantion, pretransplantation screening is very valuable. It can prevent hyperacute rejection and early antibody-mediated rejection. Guidelines recommends generic methods (Solid phase immunoassays ± CDC/FC), extended methods (SPI-SAB), and XM (CDC/FC) before and/or after lung transplantation.

Post-transplantation monitoring

Donor specific antibodies

Antibodies specifically directed against donor HLA antigens are considered as donor-specific antibodies (DSA). They can be directed against polymorphic HLA class I (HLA I), class II (HLA II), or minor histocompatibility molecules such as MICA and MICB, or even against non-HLA antigens expressed on endothelial cells, epithelial cells, or organ specific targets [45] (Fig. 2).

The reported incidences of *de novo* DSA after lung transplantation are variable. Hachem *et al*. observed an incidence of 56%, the majority of patients developed DSA in the first 90 days after transplantation [46]. However, Lobo *et al*. observed an incidence of 29.5% of DSA development with a median time of 557 days post-transplantation [47]. In a cohort analysis on 441 lung transplant recipients, 32% (n = 139) had detectable HLA antibodies [48].

Detection of DSA after lung transplantation was relatively common and was associated with earlier development of chronic lung allograft dysfunction (CLAD) or BOS [48]. Experimental data suggested that DSA had a direct effect on the pulmonary epithelium.

HLA antibodies have been associated with acute rejection in lung transplant recipients [49] and identified as the most significant risk factor for the development of BOS, which has a reported incidence of up to 50% post-transplantation [50,51]. BOS has been associated with DSA development [32]. Whether treatment to eliminate or to decrease DSA diminishes the risk of lung rejection is still unclear [32].

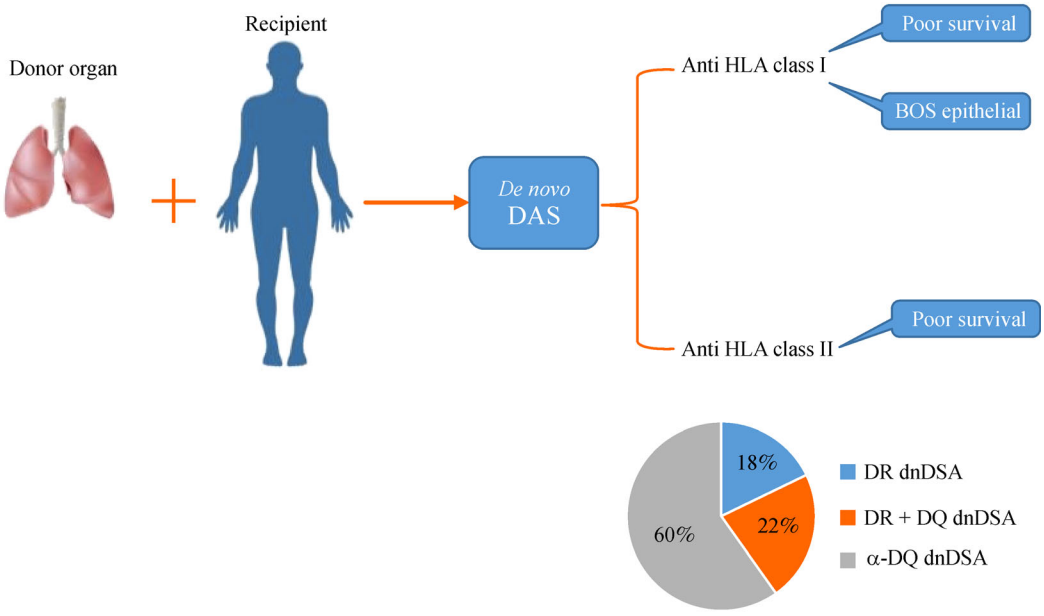

Fig. 2 *De novo* HLA-class I and -class II donor specific antibodies in the clinical outcome after lung transplantation. Both *de novo* DSA anti class I and class II can induce the poor survival of lung transplantation. *De novo* HLA-DQ DSA are more frequent than HLA-DR DSA.

Multiple factors have been reported to be significantly associated with *de novo* development of HLA antibodies, such as sex, race, positive cross match, platelet transfusion, cryoprecipitate transfusion, pre-existing HLA antibodies, CMV pneumonitis and BOS (before detection of HLA antibodies) [48]. However, following multivariate analysis, the factors identified as significant predictors for HLA antibodies were platelet transfusion, pre-existing HLA antibodies, CMV pneumonitis, and the development of BOS [48].

Some studies set out to understand the relationship between DSA development and the degree of HLA mismatch. Lobo *et al*. reported their observation of 13/44 DSA positive lung transplant patients after donor-recipient matching for HLA-A, -B, -C, -DR and -DQ, ranging from 4 loci to 10 possible loci. In the DSA group (n = 13), 10 loci were matched for HLA, but 7 loci did not match (11.5%). In the non-DSA group (n = 31), 42 loci matched for HLA, but 164 did not match (20.4%). No significant difference was noted between the groups [47].

Finally, consensus guidelines issued in 2013 discouraged transplantation of patients with a positive pre-transplantation DSA in a recent serum [52].

De novo donor specific HLA antibodies

The *de novo* development of HLA antibodies has been identified as a significant risk factor for BOS, independently of other risk factors [53]. It was observed that HLA antibodies have been associated with recurrent and high-grade cellular rejection and lymphocytic bronchiolitis [49,54].

In renal transplant recipients, the reported development of donor specific HLA antibodies by transplant patients ranges from 4% to over 50% [55]. While 30% had HLA antibodies, only 30% patients with HLA antibodies had DSA [56]. A further study observed donor specific HLA IgG in 35% of renal transplant patients [57].

In lung transplant recipients, binding of antibodies to HLA class I antigens was suggested to induce proliferation of epithelial cells in the airways, based on *in vitro* experiments, and it was hypothesized that this may contribute to the development of BOS. The proposed mechanism involved cell signaling mediated by tyrosine kinase activation [58]. Similarly, both *de novo* HLA class I and class II DSA have been associated with lessened survival [48].

A recent study of 126 lung transplant recipients also demonstrated that the significant detection of anti-HLA DSA was associated with AMR [59].

The development of HLA class II *de novo* DSA (dnDSA) is not uniform across all HLA class II antigens. In one study of 286 renal transplant recipients, 16% developed class II dnDSA overall, the majority were directed against HLA-DQ (53%) while only 20% were directed against HLA-DR [60]. Indeed, chronic rejection of renal transplants is frequently related with the presence of anti-HLA class II antibodies [61] which correlate with the incidence of AMR even in the absence of a positive T cell crossmatch [62]. Detection of antibody to HLA class II

has also been significantly correlated with worse graft outcome [63].

Relevance of HLA class I versus class II DSA

Overall, in the solid organ transplant setting, DSA recognizing either HLA class I or II are considered harmful, and recent studies have particularly underlined the association between HLA class II antibodies and graft damage whether in kidney [64,65], lung [47,66,67] or heart transplants [68].

The role of DSA and AMR in lung transplantation has been less studied than in renal or cardiac transplantation. However a recent retrospective study of a lung transplant cohort (n = 202) which compared patients with/without DSA and with/without AMR revealed that AMR was associated with CLAD and ultimately with graft survival [69]. In a retrospectively reviewed series of 86 consecutive transplants, 19 patients (22%) developed *de novo* DSA within one to six months: 6 had class I DSA only, 7 had class II DSA only, and 6 had both class I and II DSAs. In a group of 19 patients with *de novo* DSA, 14 were male and had pre-existing PRA 1%–39%. It is noteworthy that the majority of *de novo* DSA (63%) were HLA-DQ specific [70], the prevalence of HLA-DQ DSA has also been observed in renal and cardiac transplantation. In another retrospective study of lung transplant recipients, Stern reported that patients with pre-transplant DSA directed against HLA class II had a worse outcome with regard to development of BOS and mortality than patients with either HLA class I or mixed HLA class I and II DSA [71]. Once the question of HLA class II DSA has been raised, the role of individual HLA class II molecules (HLA-DR, -DQ and -DP) is also worth examining.

The analysis of Baxter-Lowe's team on 60 lung recipients demonstrated that an elevated HLA-DQ DSA (MFI $>$ 10 000) was associated with a poor clinical outcome two years after transplantation [72]. The study of 149 lung transplant recipients reported that 23% developed *de novo* DSA within three to six months after transplantation. HLA-DQ DSA were the most frequent (47%), included antibodies directed against DQB, DQA and/or a combination of DQB and DQA. DSA positive recipients had more cellular and humoral rejection than DSA negative patients (27% versus 7%) [73].

A further series of lung transplant recipients (n = 340) with HLA-antibody pre-transplant and during the first two years post-transplant was reported. DSA directed against HLA-DQ were prevalent in recipients with dnDSA (76%). Male sex and *ex vivo* lung perfusion were associated with an increased risk of dnDSA, while a higher level of HLA-DQB1 matching was protective. The detection of HLA-DQ dnDSA preceded or was simultaneous with CLAD diagnosis in all cases. Development of dnDSA was associated with a twofold increase in the risk of CLAD (HR 2.04 [95% CI: 1.13, 3.69]) and this association appeared to depend on the development of HLA-DQ DSA. These results led to the suggestion that strategies to selectively prevent or treat HLA-DQ dnDSA may significantly improve the outcome for lung transplant recipients [74]. The importance of HLA-DQ alloantibodies was also underlined by a retrospective study in which all but one patient with AMR had DSA directed against HLA-DQ [63].

Mechanisms of allograft damage by HLA alloantibodies

The mechanisms underlying allograft damage associated with HLA directed DSA in solid organ transplantation have been mainly identified in experimental models of renal and cardiac allografts and little is known of active mechanisms in lung transplantation. In organ transplantation in general, complement-dependent and -independent mechanisms have been proposed on the basis of the results of clinical observations.

In renal transplantation, antibody mediated activation of the complement cascade resulting in deposition of C4d is generally considered as an important mechanism of allograft damage. A major retrospective study pointed to a strong association of C1q binding DSA with a poor outcome of transplantation [75]. However, it has also been proposed that complement activation reflects high levels of circulating DSA rather than particular biological properties of the antibodies [76,77].

Complement activation

Complement activation has also been documented in lung transplants and associated with AMR. The diagnostic criteria for AMR in lung transplantation now include the presence of DSA and of characteristic lung histology whether or not C4d deposition is detected in the graft (in keeping with the updated Banff criteria used in renal transplantation).

Some confusion about the role of complement activation in DSA-associated allograft damage may stem from the different ways in which the complement pathway can act in addition to cell lysis, which is rarely observed in organ transplants. In cardiac allografts, complement activation acts upon the allogenic response by autocrine signaling leading to increased endothelial cell immunogenicity and increased pro-inflammatory $CD4^+$ T lymphocyte differentiation [78]. Complement activation can also alter the activity of immune cells by producing anaphylotoxins [78]. Therefore neither detection of C4d deposition, nor of C1q or C3d binding antibodies provides a complete measure of the implication of complement activation in chronic rejection.

In a single-center study, C3d and C4d deposition was reported early post-transplant in a significant proportion of 33 lung transplant patients [79]. However detection of complement components was not related to cellular or chronic rejection, nor to morphological features of AMR overall. However, an association between deposition of C3d and C4d fragments and certain morphological features of AMR was detected in a sub-group of 9 patients who developed early BOS.

Anti-HLA antibody signaling

A signaling pathway activated by HLA class I antibody binding to endothelial cells has been reported and implicates S6 ribosomal protein (S6RP) activation, the clinical relevance of this pathway was underlined by detection of activated S6RP in biopsies from cardiac transplant patients with AMR [80–82]. These data led to the proposal that S6-kinase and S6RP are potential markers of AMR in heart allografts [83]. Anti-HLA-DR antibodies activated signaling mediated by protein kinase C in heart arterial endothelial cells and activation of Akt, Erk and MEK in microvascular endothelial cells [84]. The latter study revealed that Akt activation was implicated in IL-6 secretion by endothelial cells and was induced by HLA-DR antibody binding [85]. The increased IL-6 promoted differentiation of the pro-inflammatory Th17 $CD4^+$ T cell subset by endothelial cells. This is particularly interesting because, as well as being associated with allograft damage in renal transplantation [86], the Th17 subset has been associated with the pathogenesis of BOS in an *in vivo* model of MHC class I alloantibody induced lung damage [87].

In the context of transplantation, the endothelium, in kidney or cardiac allografts, is not immunologically inert but can contribute to the immune response and this can be modified in an inflammatory environment. This may also be the case for the epithelium in the context of lung transplants. In an experimental model, HLA class II expressing endothelium activates proliferation and expansion of both pro-inflammatory (Th17) and anti-inflammatory (Treg) $CD4^+$ T cells in the presence of inflammatory cytokines. The reactivity of the endothelium was also shown in cardiac allografts where both complement-dependent and -independent mechanisms of endothelial activation resulted in expansion of pro-inflammatory T lymphocytes [88]. The nature of the allogeneic response may therefore depend on the immunogenic profile of the allograft endothelial and/or epithelial cells, and their expression of, not only HLA antigens, but also of co-stimulatory and adhesion molecules. Mezzetti *et al*. demonstrated expression of functional HLA-DR antigens on bronchial epithelial cells *ex vivo*, expression decreased in tissue culture but could be reinduced in the presence of the inflammatory cytokine interferon γ [89]. Lung allograft epithelial cells could therefore be targets for HLA class II antibody binding and activation by both complement-dependent and -independent mechanisms. Constitutive expressions of functional HLA class I and II by human lung endothelial cells have also been reported [90].

Novel strategies with the aim of preventing development of HLA class II *de novo* DSA should consider both HLA-DR and HLA-DQ loci. Indeed, defining an optimal cut-off for HLA-DR and HLA-DQ epitope mismatch load could allow assignment of allocation points favoring a low number of mismatches for both loci rather than simply a zero HLA-DR or -DQ high-resolution mismatch. The epitope mismatch load may also provide a more detailed assessment of immunological risk post-transplant regarding immunosuppressive sparing strategies or the need for post-transplant monitoring for dnDSA. Although the mechanism for how epitope load increases the risk of dnDSA development is unclear, the probability of allorecognition by a specific B cell clone is likely to heighten with a heightened mismatch number, as would the likelihood of detecting an immunodominant epitope [57].

NK cells

In addition to allogeneic T cell responses, the role of natural killer (NK) cells has been proposed in chronic rejection of kidney transplants and is supported by the detection of NK-associated transcripts in a large series of biopsies from patients with DSA. In this study 23 selective transcripts were identified only in biopsies from patients with antibody-mediated rejection, 8 of the 23 were expressed by endothelial cells and 6/23 had selective expression in NK cells so this study underlines the importance of DSA-associated transcripts expressed in NK cells or in endothelial cells [91]. Functional studies from the same group examined how activation of NK cells mediated by antibody binding to the Fc receptor CD16a led to production of soluble mediators including chemokines and pro-inflammatory cytokines. However, although the 6 NK-associated transcripts identified in biopsies were detected, they were not regulated by antibody binding to CD16a [92].

In lung transplants a potentially pathogenic pathway relies upon expression of defensins by human epithelial airway cells exposed to anti-HLA antibodies, which, in turn, increases growth factor production and epithelial proliferation in a manner resembling obliterative bronchiolitis [93]. Similarly, *in vitro* and animal fibrosis models indicate that HLA antibodies can promote profibrotic growth factors [94,95]. In renal transplantation circulating DSA have also been associated with acceleration of post-transplantation fibrosis [96].

A further mechanism was suggested following

activation of airway epithelial cells by HLA antibody binding, that of growth factor release, leading to fibroblast proliferation and epithelial cell apoptosis, all of which have been noted in the pathogenesis of BOS [97]. Studies indicated a pathogenic role for anti-HLA class I Abs in chronic rejection because higher levels of heparin binding epidermal growth factor, basic fibroblast growth factor, granulocyte monocyte colony-stimulating factor, insulin like growth factor-1, platelet-derived growth factor, and transforming growth factor-beta were observed after stimulation of aortic endothelial cells with anti-HLA class I Abs. Later studies delineated a correlation between development of *de novo* anti-MHC class II Abs and BOS [27,98].

miRNAs and transcription factors

miRNAs have been examined in the context of transplantation, and a recent study revealed a novel role of miRNAs in signaling pathways activated by anti-MHC/HLA antibodies both in a murine model of obliterative airway disease and in lung transplant patients with *de novo* DSA. Two miRNAs were identified in the mouse model and their dysregulation was confirmed in biopsies from lung transplant patients with *de novo* DSA. These miRNA were associated with upregulation of MHC class II and HLA class II molecules and it was proposed that increased HLA class II could increase allogenicity and contribute to BOS after human lung transplantation [99].

A further recent development in lung transplants was the identification of expression of a transcription factor, Zinc finger and BTB domain containing protein 7a (Zbtb7a). Elevated expression of Zbtb7a was detected in biopsies prior to clinical diagnosis of chronic rejection (compared with expression in biopsies from stable control patients). Expression of Zbtb7a was restricted to alveolar macrophages. In a mouse model, the selective disruption of Zbtb7a provided protection from chronic rejection induced by alloantibodies [100]. Regarding the mechanism of Zbtb7a function, antigen presentation by alveolar macrophages was also abrogated by selective disruption of Zbtb7a.

A summary of proposed mechanisms of the role of anti HLA antibodies in inducing lung rejection is illustrated in Fig. 3.

Elimination of DSA

Allograft rejection is associated with elevated levels of DSA and the persistence of DSA alone is a powerful predictor of late allograft loss even independently of episodes of AMR [59].

On the basis of these clinical and experimental data, it could be hypothesized that early elimination or inactivation of DSA would mitigate the risk of BOS, allow screening for DSA after transplantation and starting a preemptive treatment regimen consisting of rituximab and/or IVIG where required. Patients who developed DSA were treated with rituximab and/or IVIG, before the onset of allograft dysfunction, and approximately 60% cleared the DSA [59]. Importantly, those who successfully cleared the DSA were much less likely to develop BOS and

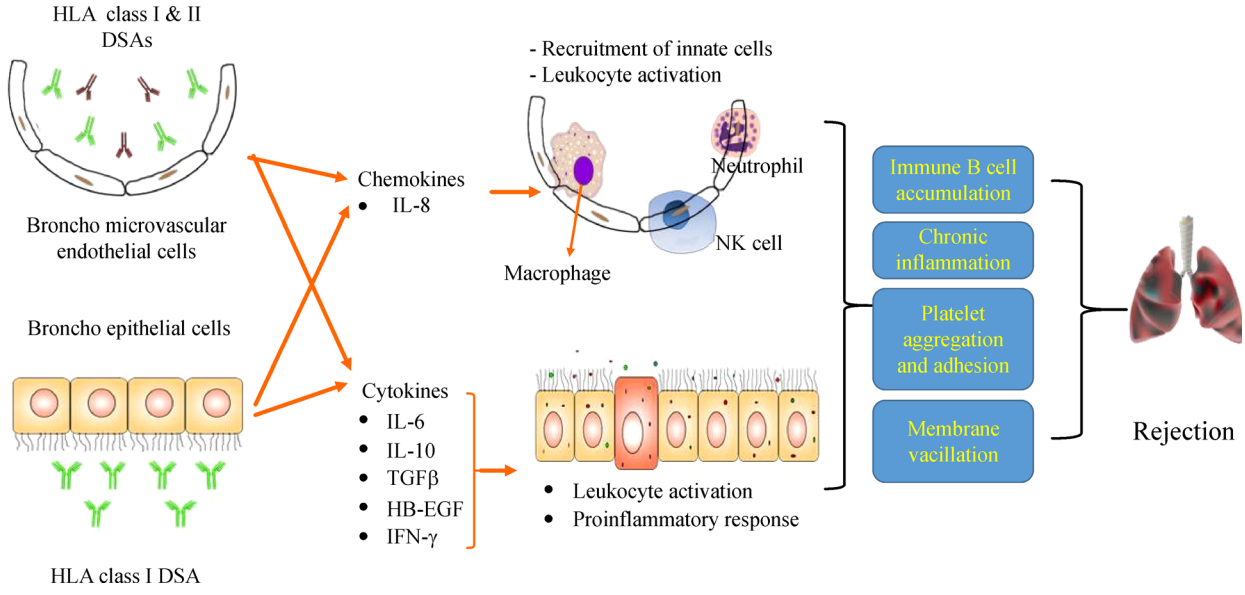

Fig. 3 Proposed mechanisms of anti HLA antibodies inducing lung rejection. Antibodies binding to "cells" can harm the allograft by several mechanisms: direct signaling in endothelial/epithelial cells may lead to increased recruitment of innate cells and/or leukocyte activation following increased production of soluble factors (and potentially by activation of adhesion molecules).

survived for longer than those who had persistent DSA. These findings suggest that DSA depletion ameliorates the risk of BOS. However, this trial was limited as it was not randomized and the treatment group was not compared to an untreated group of patients who developed DSA [59].

Accurate assessment of HLA antibody levels is required for therapeutic pre-transplantation desensitization and post-transplantation protocols to prevent AMR. The positive MFI threshold for HLA-DSA was fixed at $>$ 500. The local tissue typing laboratory grades anti-HLA DSA according to the following scale of MFIs: weak = 500–2000; moderate = 2000–8000; and strong $\geqslant$ 8000. An internationally agreed definition for pulmonary AMR has not yet been published, and a previously published definition considered that "the presence of DSA with MFI of greater than 5000 was applied as being clinically significant and a trigger for treatment in the presence of otherwise unexplained allograft dysfunction" [101]. However, the variation in MFI levels from one site to another does not simplify the application of a "cut-off" MFI for either HLA or non-HLA antibodies and it is currently difficult to define an acceptable level of circulating antibodies (Table 3).

Table 3 Mean fluorescent intensity (MFI) of HLA-DSA in lung transplantation

MFI$\geqslant$500	Positive threshold
MFI = 500–2000	Weak
MFI = 2000– 8000*	Moderate
MFI$\geqslant$8000	Strong

* MFI$\geqslant$5000 is considered as being clinically significant and a trigger for treatment [102].

It is strikingly clear that HLA typing of donor and recipient and HLA antibody monitoring pre- and post-transplantation are necessary in lung transplantation. In addition, future therapeutic progress now depends on acquiring a better understanding of pathogenic mechanisms activated and leading to allograft damage.

Discussion

The highly polygenic and polymorphic HLA complex has been extensively studied in hematopoietic stem cell transplantation wherein comprehensive HLA typing has been implemented for many years. The key role of the HLA class I and II molecules is to bind and present peptide antigens to T lymphocytes enabling the T cells to recognize and to eliminate "foreign" proteins, hence the requirement for such a high level of polymorphism. HLA mismatches may occur at the antigenic or the allelic level; characterized respectively by amino acid substitutions in both peptide binding and T cell recognition regions, or by amino-acid substitution in the peptide binding regions only [102]. Following an allotransplant donor HLA molecules are recognized by the recipient's immune system by both direct and indirect methods of triggering graft damage or even rejection. Matching of donor and recipient for HLA antigens significantly improved graft acceptance [103].

The major impact on graft loss appears to stem from the effects of the HLA-B and -DR antigens [104]. The effects of HLA-DR mismatches appear as the most important in the first 6 months after transplantation, the HLA-B effect emerges in the first 2 years, whereas HLA-A mismatches have a deleterious long-term effect on survival [105]. The role of HLA-DQ is of particular interest regarding *de novo* DSA.

Multiple studies of HLA in lung transplantation have had inconsistent results on the role of mismatches at different loci and clinical outcomes. In contrast to kidney and heart transplantation, prospective HLA matching is not possible in clinical lung transplantation, because the procedure is not considered feasible in routine practice.

In hematopoietic stem cell transplantation, it was confirmed that optimal matching for both HLA class I and II alleles can significantly decrease the severity of graft versus host disease, transplant-related mortality, and graft rejection [106,107]. Normally, HLA typing of donors should be performed before removal of donor organs to avoid extended ischemic time, which is difficult to implement in clinical practice. Because of the extensive polymorphism of the HLA system, there is a low probability of finding a well-matched recipient, zero mismatched donor-recipients are very rare, representing about 0.01% of lung recipients [18].

In lung transplantation, the median number of mismatched alleles (with respect to HLA-A, -B, and -DR) was estimated as 4 (range 0–6) [108]. The analysis from UNOS database on 23 528 adult recipients demonstrated that total HLA mismatching of $\geqslant$ 3 increased the risk of development of BOS and of death after lung transplantation. Recent reports from the ISHLT registry have included a higher number of HLA mismatches (four or more) as a risk factor for 1- and 5-year mortality in transplant recipients. Several single-center studies have also focused on the role of HLA mismatching on long-term outcome. Studies in European cohorts confirmed positive correlations between allograft failure and increasing HLA-A, -B and -DR mismatches from one to six observed for single lung, double lung, and heart-lung transplants. An increase in the risk of failure was associated with each additional mismatch with a hazard ratio of 1.10 [12]. Therefore, HLA typing even during or after lung transplantation is crucial in order to know the degree of HLA mismatch and to foresee clinical complications and to tailor anti-rejection therapeutics.

Mismatching of HLA class I has been reported to correlate with development of BOS and survival, but not with rejection whereas mismatching of HLA class II correlates with rejection (and weakly with survival). This suggests that BOS and rejection may implicate different pathways of lung injury, and factors that influence development of BOS appear to dominate as determinants of survival [109]. The effect of total HLA mismatch increases the hazard of death and BOS occurrence over the entire time period after transplantation.

A recommendation is summarized in Table 4.

Table 4 Recommendations for lung transplantation

Recommendations for lung transplantation
✓ Systematic testing of pre-existing anti HLA antibody in varity list of patients
✓ HLA typing during or after LTX to obtain the degree of mismatches in order to predict the clinical outcome risks
✓ Regularity detection of HLA antibody level of dnDSA could be outcome indicator
✓ Anti-DQ dnDSA may be biomarker of CLAD, BOS, and AMR

Conclusions

Allorecognition of HLA molecules can lead to a humoral response involving multiple antibody specificities for non-self epitopes even on a single HLA molecule. The solid organ transplant community should therefore reconsider the idea that a donor mismatched HLA molecule is a single entity. In this context, HLA-DR and -DQ epitope matching appears to outperform traditional low-resolution antigen-based matching and has the potential to reduce the risk of developing *de novo* class II DSA, thereby improving long-term graft outcome.

An alternative approach is to adopt a strategy that avoids a low number of highly immunogenic class II epitope mismatches and may be the optimal approach to minimize risk while maximizing equitable access for all individuals. The latter approach requires a major and concerted effort to further identify and validate which class II epitopes are to be considered immunodominant. It is evident that HLA analysis, typing and antibody detection, will offer clinical benefits, such as optimizing immunosuppressive prescription, predicting AMR, and improving the quality of life and survival of transplanted patients.

In the field of organ transplantation, many questions remain and this is especially true for lung transplantation, compared with other organs such as kidney or heart. Much progress has already been made in the classification of different forms of chronic lung allograft dysfunction and many centers are advancing the characterization of AMR in lung transplantation. The molecular mechanisms underlying rejection are intensively studied. Therefore, at this time where "P4" (Predictive, Preventive, Personalized, and Participatory) medicine is rapidly progressing, it is crucial to further research by (1) exploring the molecular mechanisms of lung rejection, even acute or chronic, (2) identifying specific biomarkers which are associated with the long-term clinical outcome of lung transplantation, (3) optimizing the use of immunosuppressive therapies with the aid of molecular diagnosis in order to improve the quality of life and the survival of patients after lung transplantation.

Compliance with ethics guidelines

Liya Ju, Caroline Suberbielle, Xiaofan Li, Nuala Mooney, and Dominique Charron declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol that requires approval by the relevant institutional review board or ethics committee.

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