Editorial

Allele-level HLA matching reduces early rejection in lung transplant recipients

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Nearly 40% of the genes in the human major histocompatibility complex (MHC), including human leukocyte antigen (HLA) loci associate to immune function (1,2). HLA genes evolved to be highly polymorphic to combat infection (1,2). In therapeutic transplant setting, "HLA mismatch" happens when the donor HLA on the allograft differs from the recipient. HLA mismatch leads to the activation of alloreactive T cells, which can cause acute cellular rejection (ACR) within six months of lung transplantation (3). ACR is the major risk factor for chronic lung allograft dysfunction (CLAD) (4). Mismatched donor HLA antigens are also targets for the development of *de nova* donor-specific HLA antibodies (*dn*DSA) which play augmented roles in both acute and chronic lung transplant rejection (5-8).

HLA matching is given an important priority in the national allocation of deceased-donor kidneys because of the superior survival of matched kidneys (9). Data concerning the impact of HLA matching on lung transplant outcomes is limited (10-17). Three large-scale registry studies demonstrated that survival following lung transplantation decreased as the number of HLA mismatches increased (18-20). HLA mismatch quantification is limited by 0–2 antigen values per locus, e.g., 0-antigen mismatch, 1-antigen mismatch, or 2-antigens mismatch. The number of HLA mismatches are not strictly proportional to *dn*DSA development because HLA antibodies are generated against 'epitopes', short polymorphic amino acid sequence motifs shared among multiple HLA alleles within the same and/or different loci. The shared polymorphism explains why a single HLA antigen mismatch can provoke antibodies directed against an array of HLA antigens.

For these biological reasons, it is fitting to define HLA molecular mismatch at the amino acid sequence level to quantify mismatch, which can be translated into the recipient's ability to respond against the donor's mismatched HLA antigens. Molecular matching will likely improve the precision of immunological risk assessment with *dn*DSA development as the readout for alloimmune response. Molecular matching can be scored by the physicochemical properties such as, the amino acid sequence mismatch score, the electrostatic property mismatch score, and the hydrophobic property mismatch score (21,22). The HLA matchmaker identifies "eplets", small patches of surface-exposed amino acids on mismatched HLA (either linear or discontinuous) with the ability to induce an antibody response (23,24). The quantity of mismatched eplets, or physicochemical disparities between donor and recipient alleles has been shown to correlate with *dn*DSA development, rejection, chronic glomerulopathy, and kidney graft loss (25-27). Most of these studies in kidney transplant analyzed only three (HLA-A, B, and DRB1) of the 11 known HLA loci as the expense of sequencing all loci would be cost-prohibitive. There has been no comprehensive study

investigating the role of HLA eplet or physicochemical matching on lung allograft survival.

In the issue of Annals of Translational Medicine, Zhang *et al.* describes the effects of HLA-A,B,C, DR and DQ allele-level mismatches on primary graft dysfunction (PGD) and acute rejection (AR) on 59 lung transplantations performed from April 1, 2018, to June 30, 2019 (28). The study found more mismatches at the allele-level compared to the antigen-level (8.31±1.75 *vs.* 7.19±1.61; P=0.0005) and the severity of PGD increases as the number of HLA-ABCDRDQ mismatch increases at the antigen-level as well as at the allele-level. The study also found that more HLA-DQ mismatch is significantly associated with severe PGD. One of the interesting findings from this study is the relevance of HLA mismatching in the early lung allograft rejection within a perioperative period (1 month) in unsensitized recipients (86.44% are male). However, these findings raise many questions. The paper mistakes HLA high-resolution typing mismatch with eplet mismatch. The method indicates that the eplet matching has been assessed by HLA Matchmaker program (http://www.hlamatchmaker.net), but no data on eplet mismatch is presented in the paper. The paper presents high resolution matching, and mistakenly calls it as eplet matching. The method used for high-resolution HLA typing is also a problem. The paper states that HLA allelic genotyping (-A, -B, -C, -DRB1, and -DQB1/A1) was performed by sequence-based typing (SBT) based on the Luminex technology (One Lambda, Inc., Canoga Park, CA, USA). The fact is that the Luminex-based typing used in this study is a probe-based hybridization method that detects known polymorphism and gives intermediate-level typing only. High resolution typing requires the direct sequencing of HLA genes using Sanger method or next generation sequencing methods.

In addition to HLA mismatches, the study also found a positive correlation between the severity of PGD and mechanical ventilation time or ICU time. It is unclear if the recipients with grade 3 PGD had high level of HLA-DQ mismatch, or longer mechanical ventilation time, or longer ICU stay. A multivariate analysis with a bigger cohort will address this important question. Notwithstanding these limitations, this study shows that precise degree of HLA allele matching plays a key role in the occurrence of perioperative PGD and acute rejection.

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Footnote

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