KSN 2020
FULLY VIRTUAL MEETING

Abstract Submission No. : IL-9134

Clinical application of HLA epitopes

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All alloimmunity is caused by differences between donors and recipients at the molecular level. Traditional HLA mismatch, especially HLA-DR mismatch, are correlated with outcomes in large-scale registry studies, but the ability to predict primary alloimmune risk is poor at the individual level. HLA molecular mismatch may indicate a fast, reproducible, cost-effective way to improve alloimmune risk assessment in transplantation, moving areas to precision medicine.
The HLA Matchmaker program identifies small patches of polymorphic surface-exposed amino acids named 'eplets' on each HLA allele. Eplets are defined as configurations of surface exposed polymorphic AA within 3-3.5 Å radius. HLA eplet mismatch correlates with primary alloimmune outcomes.
One approach to estimate the clinical impact of individual HLA mismatches on alloreactivity may be to quantify the total epitope load between donor and recipient. The identification of these epitopes has led to epitope-based HLA matching (EpMM). Previous studies have demonstrated the association between EpMM and primary alloimmune responses. In kidney transplantation (KT), HLA-DR/DQ EpMM showed a strong independent correlation between the development of de novo DSA , antibody-mediated rejection, transplant glomerulopathy, and poor graft survival. HLA-DR/DQ EpMM also produces synergies with medication nonadherence correlating with late rejection and graft loss, and modulates the tacrolimus trough level required to prevent DSA development.
Recent study reported that single molecule HLA-DR/DQ molecular mismatch is more correlated with the risk of dnDSA (AUC 0.84). In the Canadian cohort, antibody-verified eplet mismatches were independent predictors of transplant glomerulopathy with hazard ratios of 5.511 for HLA-DRB1 and 3.640 for -DRB1/3/4/5. Alternative computational analytics (HLA electrostatic molecular mismatch, or amino acid molecular mismatch) have similar performance for DSA free survival. In addition, software has recently been developed to assess the likelihood of donor HLA peptide fragments being presented by the unique Class II HLA molecules in individual recipients (Predicted Indirectly ReCognizable HLA class II; PIRCHE-II).
Epitope matching can be used in clinical practice to avoid future allosensitization due to de novo DSA and to select the appropriate allograft for highly sensitized patients through virtual crossmatch.
This session will discuss an approach to the clinical application of eplets mismatches in KT.