Quantitative Analysis of Eplet Load in Heart Transplant Rejection: Evaluating the Significance of Mismatches Across Different HLA loci

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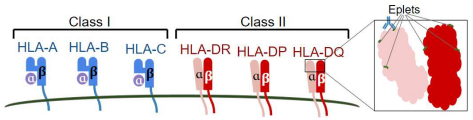
Background

- HLA (or MHC) proteins are surface protein complexes that are essential for the adaptive immune system
- There are two classes of HLA, each with three receptors: Class I contains HLA-A, -B, and -C; while Class II contains HLA-DR, -DP and -DQ.
- Different variants of each receptor exists. If donor and recipient variant of receptor don't match (an event referred to as an **antigen mismatch**), rejection might occur[1]
  - **Eplets** are residues on the surface of receptors that differ between variants and can lead to antibody development

Figure 1: A schematic representation of the different HLA receptors and eplets.



Research Questions

1. Does eplet mismatch load associate with rejection?
2. What type of eplet mismatches are most important and how much increased hazard (chance of failure) do they confer?
3. Do eplet or antigen mismatches provide a more accurate model for predicting transplant outcome?

Significance of the Study

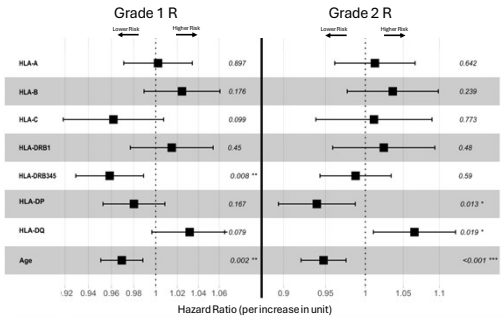
- Eplet matching may improve heart transplant outcomes and reduce incidence of rejection
- Eplet load could be used for personalized immunosuppressant dosing, based on risk groups, should they play a significant role in rejection
- Eplet matching is more expensive and time-consuming than antigen matching, it is useful to know if it confers additional predictive accuracy

Methodology

- High resolution genotyping was completed on 108 heart transplant donor-recipient pairs. Antigen and eplet matching was performed
- Routine heart biopsies from all patients (taken at 1, 2, 3, 4, 6, 8, 10, 12, and 52 weeks) were given a ISHLT ACR (2005) grade[2]: **Grade 0** – No rejection, **Grade 1 R**– mild rejection, **Grade 2 R**– moderate rejection and Grade 3 R– severe rejection
- Univariate and multivariate (with every variable) Cox proportional hazards models were constructed using age, HLA-A, -B, -C, -DRB1, DRB3/4/5, -DP, -DQ eplet mismatches for time to first instance of Grade 1 R or 2 R rejection. This was repeated with antigen mismatches for comparison

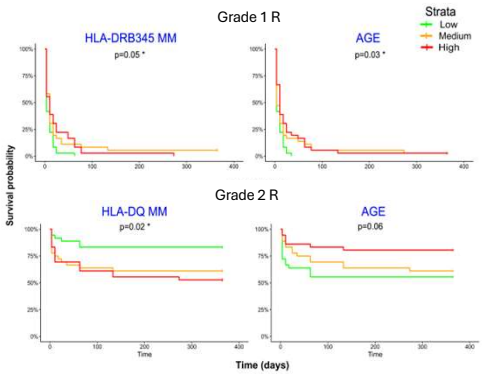
Results

Figure 2: Forest plots depicts the risk factors for rejection. The graph on left represents the hazard ratios of Grade 1 R rejection for a given increase in the respective variable found using a multivariate model. The plot on the left represents hazard ratios of another multivariate model for Grade 2 R rejection. Bars around each point show a 90% confidence interval and p-values are given of on the right of the bars. Asterisks beside p-values mark significance ($p<0.05$).



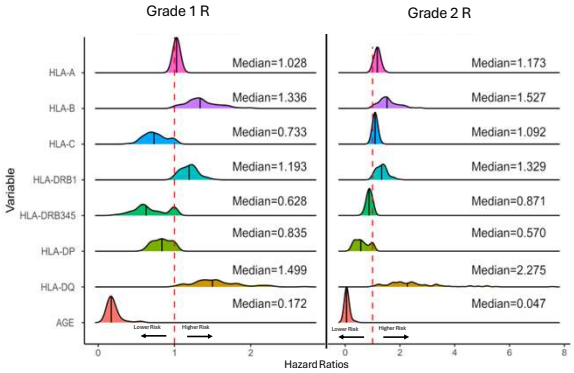
- Increased *HLA-DRB3/4/5 eplet mismatches* and *Age* reduce risk of Grade 1 R rejection
- *HLA-DQ* increases risk of Grade 2 R rejection, while *HLA-DP* eplets and *Age* reduce this risk

Figure 3: Kaplan-Meier curves depict survival probabilities (chance of not suffering any Grade 1 R or 2 R rejection) at different times for significant variables. Individuals were stratified into the groups "low" (bottom 33% percentile), "medium" (34%-66% percentile), and "high" (top 67%) for HLA-DQ, -DRB3/4/5 eplet mismatches and age. Log-rank tests were performed to obtain the significance of the differences between the survival curves



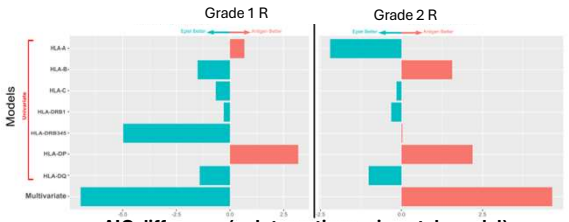
- "Low" *HLA-DQ eplet mismatches* lead to increases in time to Grade 2 R rejection; however, little difference exists between "Medium" and "High"
- *Age* leads to increases in survival probabilities
- "Low" *Age* and *HLA-DR3/4/5 mismatches* lead to shorter times until Grade 1R rejection

Figure 4: Bell curves represent the distribution of total hazard ratios conferred by each variable for individuals in this study. Median hazards ratios are shown on the right. The hazard ratios were obtained from multivariate Cox proportional hazards models for Grade 1R (left) and Grade 2R (right).



- Age is the greatest diminisher of risk, higher ages correspond to lower risk of Grade 1 R and 2 R rejection
- HLA-DRB3/4/5 strongly reduces risk of Grade 1 R rejection
- HLA-DQ is the greatest risk factor for both Grade 1 R and 2 R rejection

Figure 5: A Bar graph depicts difference in Akaike Information Criterion (AIC) between eplet and antigen mismatch models. AIC represents prediction, and lower is better. Blue bars show eplet models have lower error, while red show the corresponding antigen model may be superior



- Inconclusive whether antigen or eplet mismatches are superior: eplet mismatches generally predict Grade 1 R rejection better, but Grade 2 R may be better modeled by antigen in some cases

Conclusion

Eplet mismatches are good predictors of Mild (Grade 1R) and Moderate (Grade 2R) rejection, with HLA-DQ substantially increasing risk, and HLA-DP and –DR3/4/5 potentially having protective effects.

References

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