AAV delivery of PD-L1 with concomitant CTLA-4 immunoglobulin attenuates acute cellular rejection in a rat lung transplant model

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Introduction

- Acute cellular rejection (ACR) is a frequent and significant complication in lung transplant (LTx) recipients and the leading predictor of chronic lung allograft dysfunction (CLAD)1. Utilizing viral vectors to deliver genes that generate proteins with anti-inflammatory or immunosuppressive properties to donor lung allografts is an attractive strategy to prevent ACR.

- Primary Goal: To evaluate whether Programmed Death Ligand 1 (PD-L1) gene transduction via AAV9 vector can be used to abrogate acute rejection in a clinically relevant, allogeneic LTx model.

Methods

- Orthotopic left LTx was performed by implanting grafts procured from Brown Norway donors into Fischer F344 recipients using a “cuff” technique3 (n=11).
- Upon graft procurement, AAV9 vectors were administered during static cold storage. Experimental animals received 4e11 VG AAV9 PD-L1 through the left bronchus (n=6). Negative controls received no viral vector. Both cohorts received a 500 ug dose of CTLA-4 immunoglobulin (Abatacept) on the first post operative day (POD1) and were sacrificed on POD14. Tissue was collected and stained with PD-L1 IHC or H&E to assess gene expression or ACR, respectively. ACR was graded by a blinded lung pathologist following ISHLT guidelines.

Conclusions

- We demonstrate successful transgene expression using a novel AAV9 PD-L1 vector during static cold storage in an allogeneic rat lung transplant model.
- Difference between groups indicates potential for using transgenic PD-L1 to protect against ACR after lung transplantation.

Next Steps

- Further studies will elucidate the inflammatory effect of the viral vector itself by incorporating a control group that receives the same dose of viral vector carrying a reporter gene (luciferase).
- Intervention dose, AAV serotype and cell target, and concomitant immunosuppression regimen can likely be further optimized to better abrogate ACR after lung transplantation.

References