Identifying self antigens targeted by T cells in immunotherapy-induced fatal myocarditis

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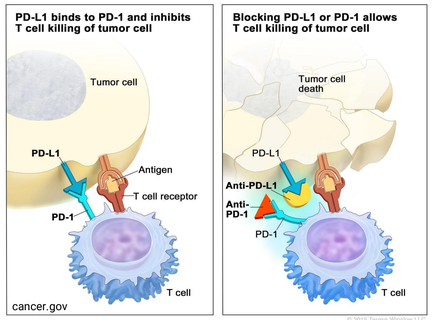
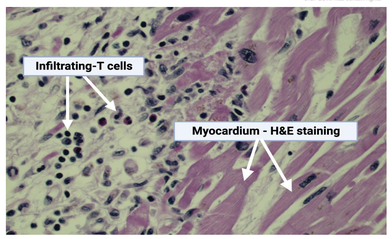
Abstract

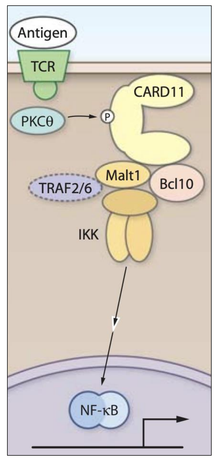
Immune checkpoint inhibitors (ICIs) are cutting-edge technologies blocking immune checkpoints (PD-1/PD-L1 and CTLA-4) and promoting immune responses to tumor cells. ICI drugs have been shown to be very effective as a cancer therapy for malignant melanoma, non-small cell lung cancer, and head and neck squamous cell carcinoma, among other cancer types. However, over-activation of the immune system may cause side effects known as immune-related adverse effects (irAEs), which are characterized by severe inflammation, including infiltration by T cells into various tissues. An understanding of the mechanism of irAE development remains incomplete. Here we seek to identify the specific antigens targeted by tissue-infiltrating T cells in patients who developed fatal ICI-induced myocarditis. A more complete understanding of the mechanism of irAEs may lead to the development of anti-T cell therapies that could mediate the danger of irAEs to cancer patients.

Background

- ICI drugs activate T cells by blocking PD-1/PD-L1 and/or CTLA-4, leading to T cell-targeting of tumor cells and increased patient survival.
- Although ICI drugs are effective in the treatment of advanced cancers, including metastatic melanoma, lung cancer, kidney cancer, bladder cancer, and head and neck cancers, severe treatment-limiting irAEs occur in approximately 15% of patients after PD-(L)1 blockade and almost 55% of patients with combination PD-(L)1 and CTLA-4 blockade.
- The mechanism of irAEs is not fully understood.





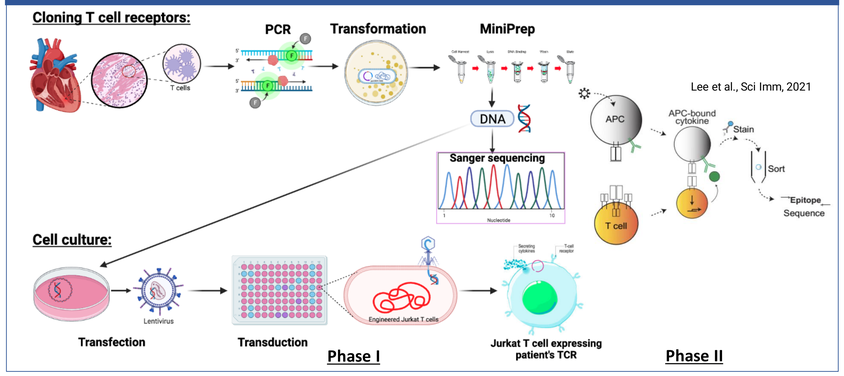


Wegener et al. Sci Sig, 2007

Hypothesis

We hypothesize that the target antigen of T cells in fatal ICI-induced myocarditis is a self antigen expressed by cardiomyocytes. This self antigen may be aberrantly expressed by the tumor cells, leading to T cell activation, and subsequently a lethal irAE.

Methods



Results

Figure 1: Identifying TCRs via next generation sequencing (NGS). Graph of NGS data from irAE-affected myocarditis tissue showing the frequency of TCRα and TCRβ V/J gene segment usage of T cells infiltrating into myocardium. This data is consistent with the clonal expansion of specific T cells in patient tissue.

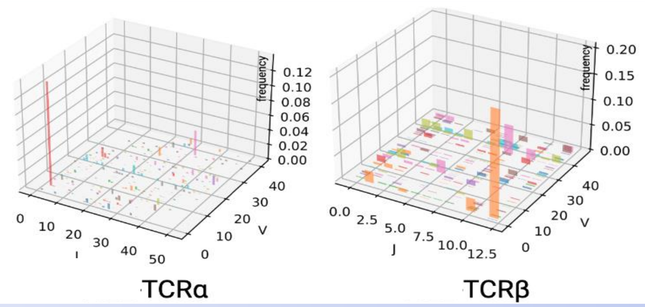
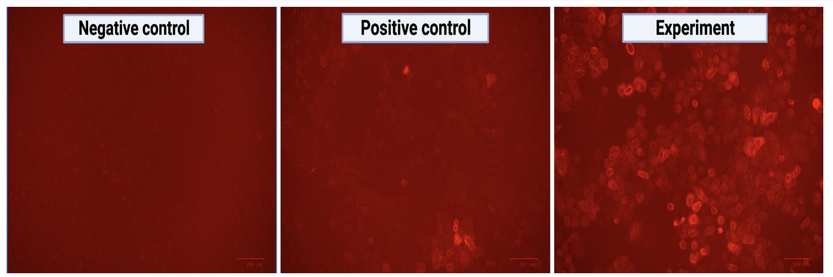


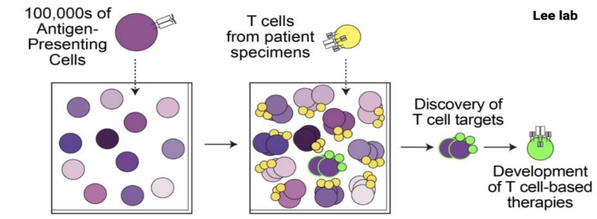
Figure 2: Engineering T cells to overexpress CARD11 and LTBR enhances downstream signaling leading to increased cytokine signal. Cytokine-capturing APCs (antigen-presenting cells) were co-cultured with T cells transduced with *CARD11* and *LTBR* (Experiment) or without these genes (Positive control). Cells were then stained with a PE anti-IL2 antibody and imaged under the fluorescence microscope. APCs alone are also shown (Negative control).



Conclusion

- We successfully HLA typed the patients and cloned their HLA genes to express in our antigen-presenting cells *in vitro*.
- We successfully identified clonally-expanded T cell receptors that may be responsible for the lethal irAEs.
- We engineered our T cell line to overexpress *LTBR* and *CARD11* to promote T cell activation in our *in vitro* co-culture system.

Future Directions



- We will screen a library of putative antigens expressed by cardiomyocytes against the T cell receptors that we identified from irAE patients.
- *LTBR* and mutant CARD11 can be used in these co-culture experiments to drive T cell activation and enhance the cytokine signal in our assay.
- We can use our high-throughput T cell identification technology to not only study the mechanism of irAEs but also of other autoimmune diseases as well as the targets of tumor-infiltrating T cells in cancer patients.

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