

POSTER PRESENTATION

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Specific increase in T cell potency via structure-based design of a T cell receptor for adoptive immunotherapy

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Adoptive immunotherapy with antigen-specific T lymphocytes is a powerful strategy for cancer treatment. However, most tumor antigens are non-reactive “self” proteins, which presents an immunotherapy design challenge. Studies have shown that tumor-specific T cell receptors (TCRs) can be transduced into normal peripheral blood lymphocytes, which persist after transfer in about 30% of patients and effectively destroy tumor cells. Still, recent clinical trial with affinity-enhanced TCRs has resulted in severe effects due to cross reactivity to an unrelated peptide. Thus, the challenge for targeted T cell therapy remains to increase T cell potency in order to improve clinical responses and ensure on-target specificity by avoiding unwanted cross reactivity. We used structure-based design to predict point mutations of a TCR (DMF5) that enhance its binding affinity for an agonist tumor differentiation antigen-major histocompatibility complex (pMHC), Mart-1(27L)-HLA-A2, which elicits full T cell activation to trigger immune responses. Structural based approaches have been used to increase TCR affinity, however their potential cross-reactivity has not been reported. Here, we analyzed the effects of selected TCR point mutations alone and in combination on T cell activation potency. Further, we analyzed their specificity and cross-reactivity with related antigens presented by different melanoma cell lines and donor-derived antigen presenting cells. Our structure-based approach allowed us to rationally design sequence substitutions that improve binding in contact areas between the TCR and pMHC without increasing cross-reactivity with a wide variety of self-antigens. We identified and evaluated point mutations

in critical TCR positions resulting in more potent T cell activation but maintaining overall specificity. When double and triple combination mutations were introduced, they exhibited an additive enhancement that further improved T cell activation while retaining a high degree of specificity.

Conclusions

Such affinity-optimized TCRs could potentially be used in adoptive immunotherapy to treat melanoma while minimizing adverse autoimmunity effects.

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