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Poster presentation

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Background

Co-stimulatory molecules play a critical role in the development of cellular immunity. Understanding how co-stimulatory pathways interact and influence the immune response is critical for the generation of an effective HIV vaccine. We evaluated the ability of intravenous administration of blocking monoclonal antibodies (mAb) directed against the negative co-stimulatory molecule, CTLA-4, and an agonist mAb directed against the positive co-stimulatory molecule, 41BB, to augment intramuscular SIV DNA immunizations. We then tested the ability of these responses to impact a SIVmac251 challenge.

Methods

Groups of six cynomologous macaques were immunized intramuscularly five times with consensus SIV gag, env, and pol plasmid DNA. On the day of each immunization, as well as two days later, macaques were infused with 10 mg/kg of an anti-41BB mAb, an anti-CTLA-4 mAb, both, or without antibodies. Cellular immune responses were evaluated by ELISpot, CFSE proliferation, and ICS for polyfunctionality. Three months following the final immunization, the animals were intra-rectally challenged with a high-dose of SIVmac251.

Results

Following immunization, the groups infused with the anti-41BB mAb had enhanced IFNγ responses compared to the DNA group (average 7,500 and 5,000 SFU/10^6 PBMCs, respectively). Although CTLA-4 blockade alone did not enhance IFNγ responses it did increase T cell proliferation. The combination of mAbs enhanced the magnitude of the polyfunctional $CD8^+$ T-cell response. Following challenge, the group that received both mAbs had a significant, 2 log, decrease in plasma viral load compared to the naïve group (4.16×10^5 and 5.13×10^7 viral copies/ml of plasma, respectively, $p = 0.0266$, Kruskal-Wallis).

Conclusion

These data demonstrate the utility of targeting co-stimulatory pathways to modulate cellular immunity following DNA vaccination. CTLA-4 blockade and 41BB stimulation during immunization resulted in a significant decrease in peak viral load following SIVmac251 challenge. Our results represent a considerable improvement in the efficacy of naked intramuscular DNA vaccines in macaques.