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P19-55 LB. Effective control of a pathogenic SIVmac239 challenge by a novel heterologous mucosal prime and intramuscular boost vaccine strategy

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Background

The failure of a recombinant adenovirus serotype 5 (rAd5) vector-based vaccine for HIV-1 in a phase 2b efficacy study in humans calls for efforts to develop novel vaccination strategies.

Methods

In this study, we developed a recombinant replication-competent modified vaccinia Tiantan (MVTT), namely $rMVTT_{SIVgpe}$, as a mucosal vaccine expressing SIVmac Gag, Pol and Env. The immunogenicity and efficacy of $rMVTT_{SIVgpe}$ was studied in combination with an rAd5-based vaccine $rAd5_{SIVgpe}$ in Chinese macaques (Macaca mulatta) without the protective MHC class I allele Mamu-A*01. $rMVTT_{SIVgpe}$ was given through intranasal and oral inoculations whereas $rAd5_{SIVgpe}$ was given through intramuscular injection. Four macaques in each of the four study groups received the following prime and boost vaccinations: $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$; $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$, twice; $rAd5_{SIVgpe}/rAd5_{SIVgpe}$; and placebo controls, respectively.

Results

We found that the heterologous $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$ regimen elicited cellular immune responses with enhanced magnitude, breadth, sustainability, and polyfunctionality when compared with the homologous $rAd5_{SIVgpe}$ regimen. Higher levels of neutralizing antibody (Nab) responses were also induced by the $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$ regimen. These Nab responses, however, neutralized SIVmac1A11 but not SIVmac239. The additional round of $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$ vaccinations did not enhance the immune responses further. After intrarectal challenge with a pathogenic and Chinese macaque-adapted SIVmac239 (5×10^5 $TCID_{50}$ per animal), one of four monkeys vaccinated with the $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$ regimen was fully protected whereas the rest showed an average of 1.96 log and 2.22 log reduction of peak and set-point (6 weeks post challenge) viral loads as compared with control animals.

Conclusion

These data demonstrate that the $rMVTT_{SIVgpe}/rAd5_{SIVgpe}$ regimen induced durable partial immune control of a pathogenic, neutralization-resistant SIVmac239 challenge. Our findings have critical implications for further optimization of vaccination strategies against HIV-1 by engaging the mucosal immune system.