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Evidence for Env-V2 sieve effect in breakthrough SIV $_{MAC251}$ infections in rhesus monkeys vaccinated with Ad26/MVA and MVA/Ad26 constructs

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Background

We had previously shown that rhesus monkeys receiving Ad26/MVA and MVA/Ad26 vaccines expressing SIV$_{SME543}$ were protected against SIV$_{MAC251}$ challenge (doi:10.1038/nature10766). Protection was associated with Env-specific binding ELISA antibody responses, including V2-specific antibodies.

Methods

We amplified 66 sequences from the SIV $_{MAC251}$ challenge stock, and 409 near-full length genomes from 13 vaccine and 13 control monkeys. A series of pre-specified phylogenetic and statistical tests for sieve effects was performed.

Results

The mean pairwise AA diversity among the 66 SIV-$_{MAC251}$ Env sequences was 0.38%, and they differed from the vaccine strain SIV $_{SME543}$ (Env) by 21.94%. The repeated low-dose challenge resulted in infections with an average of 1.7 founder variants - with no evidence that the vaccine restricted the number of variants ($p = 0.813$). We explored whether the vaccine induced a sieve effect, i.e. whether breakthrough viruses differed between the vaccine and control groups. There was no difference for full-length Env sequences. Focusing on Env segments preferentially recognized by vaccinated monkeys in antibody arrays, we identified a sieve effect in the Env-V2 segment AA163-193: sequences from vaccinated animals were more divergent from the vaccine SIV$_{SME543}$ or from the challenge stock SIV$_{MAC251}$ than sequences in control animals ($p \leq 0.002$).

Conclusion

The sieve effect in Env-V2, combined with Env-V2-specific binding antibodies identified as a correlate of protection against SIV $_{MAC251}$ acquisition in the study, provide evidence supporting the importance of protective responses directed against the Env-V2 region.

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