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Poster presentation

P17-13. Hexon hypervariable regions 4–7 contain important Ad5-specific neutralizing antibody epitopes

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Background

The immunogenicity of adenovirus serotype 5 (Ad5) vectors is suppressed by pre-existing neutralizing antibodies (NAbs) that are directed primarily against the hexon hypervariable regions (HVRs). We previously reported that replacing all 7 HVRs of the Ad5 hexon protein with those from the rare serotype Ad48 resulted in a chimeric Ad5HVR48(1–7) vector that evaded pre-existing immunity in preclinical studies.

Methods

An intermediate Ad5HVR48(1–3) vector was constructed by replacing only the first three HVRs of Ad5 with those of Ad48. C57/BL6 mice, either naïve or preimmunized twice with 10^{10} vp of Ad5Empty, were immunized with 10^{9} vp of Ad5, Ad5HVR48(1–3) or Ad5HVR48(1–7) vectors expressing SIV-Gag. Gag-specific CD8+ T cell responses were measured by tetramer binding, ELISPOT and ICS assays following immunization. Human and murine sera were also assessed for neutralizing antibody responses against Ad5, Ad5HVR48(1–3), Ad5HVR48(1–7), and Ad48.

Results

Ad5, Ad5HVR48(1–3), and Ad5HVR48(1–7) vectors expressing SIV-Gag proved comparably immunogenic in mice by tetramer, ELISPOT, and ICS assays. In the presence of Ad5-specific pre-existing immunity, however, the immunogenicity of Ad5 and Ad5HVR48(1–3) vectors was abrogated and only Ad5HVR48(1–7) was immunogenic. NAb titers in Ad5-vaccinated mice as well as in humans from sub-Saharan Africa were stratified as follows: Ad5 >Ad5HVR48(1–3) > Ad5HVR48(1–7) > Ad48.

Conclusion

The serology studies indicate that a fraction of Ad5-specific NAbs are directed against HVR 1–3. However, the Ad5HVR48(1–3) vector was unable to evade Ad5-specific NAbs in vivo. These data indicate that HVR 4–7 contain key Ad5-specific NAb epitopes.