



ORAL PRESENTATION

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Occult replication of a conditionally-live attenuated SIV profoundly upregulates T effector memory cell frequency

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Background

The most potent protection against infection with virulent SIV, including protection against mucosal challenge, is conferred by “vaccination” with live attenuated virus. Although this approach is precluded for HIV because of safety concerns, understanding the mechanisms of superinfection resistance may inform rational vaccine design.

Materials and methods

In order to uncouple antigen exposure from active viral replication we compared peripheral and intestinal T cell phenotype and SIV peptide-specific responses following infection of macaques with wild type SIVmac239, attenuated SIVmac239 Δ *nef* or with a doxycycline (dox)-conditional replication variant of SIVmac239 Δ *nef* designated SIVrtTA. Global (antigen-non-specific) T cell phenotype was assessed for central memory (T_{cm}) (CD28⁺CCR7⁺CD95⁺), transitional (CD28⁺CCR7⁻CD95⁺) and effector memory (T_{em}) (CD28⁻CCR7⁻CD95⁺) and SIV-specific T cell responses were measured by detection of TNF- α , IFN- γ , IL-2 and IL-17.

Results

In animals in which on-going virus replication was permitted, albeit not detectable in the systemic circulation, (SIVrtTA + dox & SIVmac239 Δ *nef*), the proportion of CD4 and CD8 T_{cm} and transitional T cells were reduced in the majority of animals while T_{em} proportions increased. In animals infected with SIVrtTA in

which dox had been withdrawn for 8 weeks prior to analysis, these changes were not seen. Moreover animals infected with wild type virus had elevated CD4 and CD8 T_{cm}. Analysis of gut mucosal homing (α 4⁺ β 7⁺ and β 7⁺) T cells showed similar polarised changes.

Conclusions

Overall, we found that active occult replication of SIVrtTA and SIVmac239 Δ *nef* had a profound impact on global T cell phenotype and antigen-specific polyfunctionality in the periphery and the gut. The use of these SIV mutants will contribute to the understanding of the mechanisms of superinfection resistance.

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