Protection from a Pathogenic Heterologous SIV by Elite Controllers of SIVmac239ΔGY

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BACKGROUND

- Correlates of protection from diverse viral strains are sorely needed to inform rational HIV vaccine design.
- Pigtail macaques (PTM) infected with SIVmac239 ablated of a highly conserved trafficking signal, leads to elite viral control in nearly all animals in the absence of neutralizing antibodies. (Breed, M. et al. J Virol. 89: 10156, 2015. PMID: 26223646)
- **We hypothesized** that infection with this virus (termed ΔGY) would induce immunity capable of protection from challenge with heterologous SIVsmE660, which is highly pathogenic in PTM, enabling the identification of effective immune responses that may be recapitulated in future vaccines.

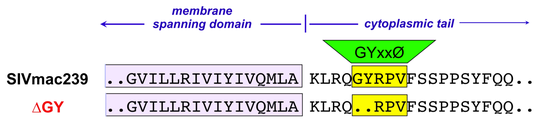


Figure 1: Construction of the ΔGY virus

METHODS

- Cohorts of ΔGY-controlling PTM were challenged i.v. with SIVsmE660 at various time points after ΔGY infection ranging from ~30 weeks (short-term, n=2) to >5 years (long-term, n=6). Naïve control PTM (n=5) were also challenged.
- Plasma viral loads were followed using an assay capable of discriminating between SIVmac239ΔGY and SIVsmE660 RNA.
- Innate and virus-specific adaptive cellular responses in blood and mucosal sites were tracked over time before and after SIVsmE660 challenge to identify correlates.

Work in Progress

- Transcriptomic profiles before and after SIVsmE660 challenge are being assessed in blood and GI tract, including sorted CD4 and CD8 T cells, NK cells, monocytes, and B cells (see 2021 CROI abstract 2295, *Ribeiro et al*.)
- Anamnestic CD4 and CD8 T cell epitopes are being mapped to identify responses that cross recognize diverse challenge viruses.

Elite control of SIVmac239ΔGY confers protection from heterologous SIV in the absence of neutralizing antibodies.

RESULTS

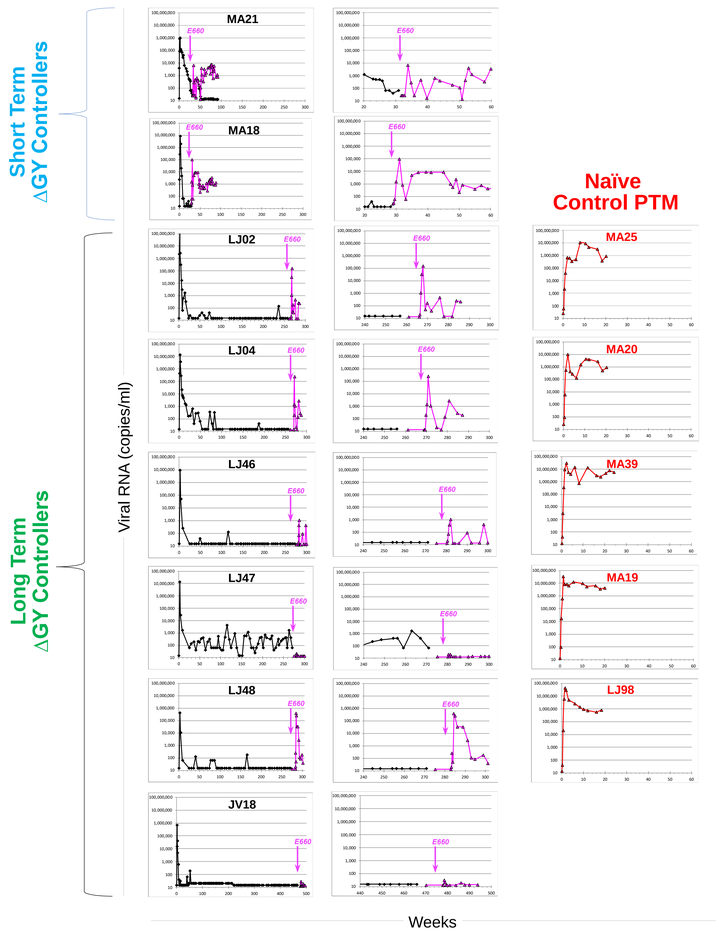


Figure 2: SIV plasma viral loads during ΔGY control and SIVsmE660 challenge. Two PTM (MA21 and MA18) infected with ΔGY for 30 weeks (**short term ΔGY controllers**) and 5 PTM infected with ΔGY for more than 5 years (LJ02, LJ04, LJ46, LJ47, and LJ48) and 1 for more than 9 years (JV18) (**long term ΔGY controllers**) were challenged with heterologous SIVsmE660, which is highly pathogenic in PTM. ΔGY (**black**) and SIVsmE660 (**magenta**) plasma viral RNA levels are shown. The assay used to detect SIVsmE660 RNA is specific for this virus and does not detect ΔGY RNA. The middle column shows a more focused view of the SIVsmE660 challenge phase to highlight control of this challenge. Right column shows 5 naïve PTM inoculated with SIVsmE660 (**red**).

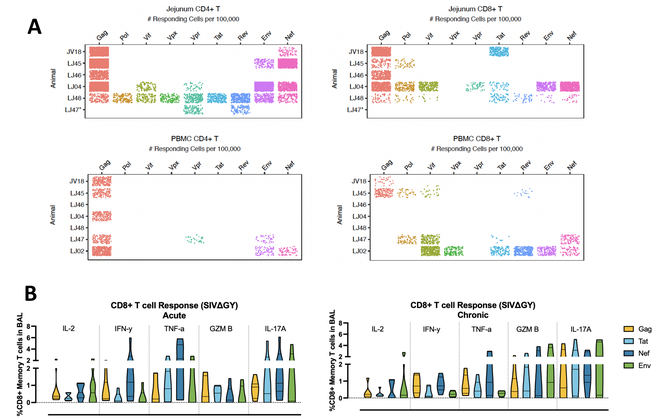


Figure 3: Cellular immune responses to SIVmac239ΔGY in mucosal sites and blood. Intracellular cytokine staining on PBMC and jejunum to identify proteins targeted by CD4 and CD8 T cells, A. Magnitude of the response is represented by spot density. Bronchoalveolar lavage was used to assess cytokine profiles of antigen-specific T cells, B.

CONCLUSIONS

Our data thus far demonstrate:

- ΔGY infection induces potent cellular immunity in blood and mucosal sites that are capable of controlling a heterologous and highly pathogenic SIV challenge and some of these responses are non-classical (see supplemental figure)
- The determinants of immune control may require time to mature. Short term ΔGY controllers exhibited partial control of E660 but this control remained robust for at least 1 year.
- The development of cellular immune responses that can lead to robust protection over time offers a unique opportunity to dissect immunological mechanisms of protection that may provide important concepts for the development of effective vaccines.

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