Retrovirology

BioMed Central

Oral presentation

S021-04 OA. A large-scale analysis of immunoglobulin sequences derived from plasmablasts/plasma cells in acute HIV-1 infection subjects

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from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):O4 doi:10.1186/1742-4690-6-S3-O4

This abstract is available from: http://www.retrovirology.com/content/6/S3/O4

Background

In acute HIV-1 infection (AHI) there are infection-induced polyclonal shifts in blood and bone marrow B-cell subsets from naïve to memory cells and plasmablasts/plasma cells (PCs) coupled with decreased numbers of naive B cells. To study the initial antibody response to HIV, we have used recombinant technology to create a database of PC antibody sequences derived from 3 early stage AHI subjects.

Methods

Using computational methods that determine the germline rearrangement of immunoglobulin genes, we have characterized the somatic population genetics of the nucleotide sequences of 850 recombinant Ig VH and VL pairs derived from bone marrow and blood of three AHI subjects from approximately day 17, day 20 and day 30 after HIV-1 transmission.

Results

We found that the Ig genes from the 20 day AHI PC showed extraordinary clonal relatedness among themselves; a single immunoglobulin (Ig) clone comprised of 50 members, with antibodies specific for HIV-1 Env gp41. Ninety percent of the 850 Ig VH chains from AHI antibodies were class-switched and either IgG or IgA. Most of the PC antibodies from AHI were not HIV specific with only 43/850 (5.6%) HIV gp41 specific. The HIV-1 specific antibodies showed a bias towards the usage of VH3 compared to germline VH3 usage. While the HIV-specific Igs primarily used IgG3 HCs, the non-HIV-specific Igs were primarily IgAs. HIV-specific but not influenza specific antibodies had a marked kappa skewing with a HIV Ig kappa/lambda ratio of 11.25. The non-HIV-specific VH and VL Ig genes had mutation frequencies of over 6% while the non-HIV-specific Ig genes had mutation frequencies of ~4.5%.

Conclusion

These data suggest that HIV induces activation of previously triggered and mutated non-HIV-1 memory B cells and demonstrates the profound perturbation of the B cell arm of the immune system soon after HIV-1 transmission.