Innate impairment during SIV infection alters ZIKV viral pathogenesis

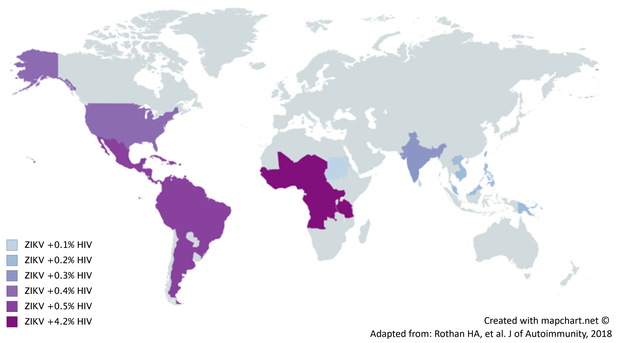
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Jennifer Tisoncik-Go[1,2,3], Thomas B. Lewis[1, 4], Skyler Niemeyer[4], Andrew Gustin[1,2], Rene A. Ruiz[4], Paul Kim[4], Kai Hubbell[4], Kathleen Voss [1, 2, 3], Jin Dai[1, 2, 3], Naoto Iwayama[1], Chul Ahrens[1], Solomon Wangari[1], Robert Murnane[1], Kathryn A. Guerriero[1], Michael Gale Jr [1, 2, 3, 5], Deborah H. Fuller[1, 4], **Megan A. O'Connor[1, 4]**

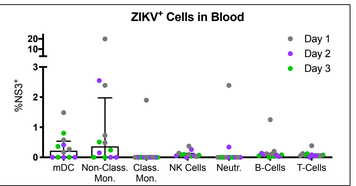
[1]Washington National Primate Research Center, University of Washington (Seattle, Washington), [2]Department of Immunology, University of Washington (Seattle, Washington), [3]Center for Innate Immunity and Immune Disease (CIIID), University of Washington (Seattle, Washington),[4]Department of Microbiology, University of Washington (Seattle, Washington), [5]Department of Global Health, University of Washington (Seattle, Washington)

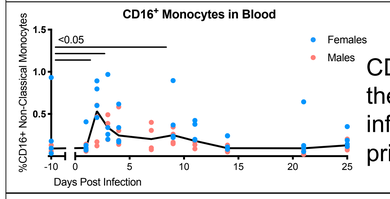
Background and Hypothesis

Background: Flaviviruses are in >100 countries across the globe and in areas with endemic HIV. Despite the occurrence of large flavivirus outbreaks and geographic overlap in countries with high HIV prevalence, there is insufficient research to determine the risks of flavivirus coinfection in people living with HIV and the subsequent impact on co-morbidities.



CD16⁺ monocytes are major ZIKV blood cellular targets

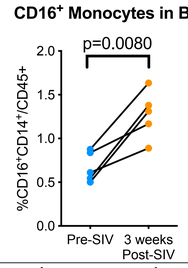




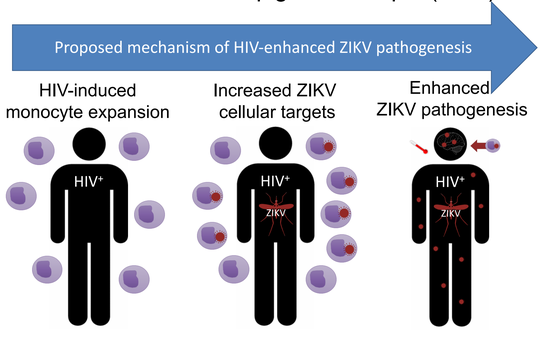
CD16⁺ monocytes expand in the periphery during ZIKV infection in non-human primates

CD16⁺ monocytes expand during HIV and SIV infection and can harbor virus

Monocytes mediate HIV and flavivirus invasion into the central nervous system



Hypothesis: Enhanced ZIKV pathogenesis occurs in people living with HIV and we experimentally tested this hypothesis using an SIV-ZIKV coinfection pigtail macaque (PTM) model.



Results

Figure 1. PBMC from SIV-infected PTM are less permissive to ZIKV infection in vitro

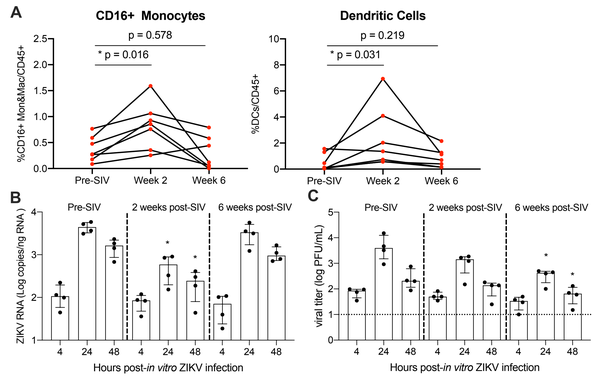


Figure 1. (A) Frequency of CD16+CD14+ monocytes and macrophages (left panel) and dendritic cells (right panel) in blood from uninfected and SIV-infected pigtail macaques. Wilcoxon matched-pairs signed rank test, p-values ≤ 0.05 considered significant. (B-C) Peripheral blood mononuclear cells (PBMC) were isolated from pigtail macaques prior to and at 2 and 6 weeks post-SIV infection and infected in vitro with ZIKV Brazil at an multiplicity of infection (MOI) of 2. Cells and supernatant were harvested 4, 24, and 48 hours post infection. (B) Quantitative real-time PCR (qRT-PCR) for ZIKV RNA in PBMC. (C) Plaque assay for infectious virus. (B-C) Medians with interquartile ranges are shown. Kruskal-Wallis test versus pre-SIV levels, p-values * ≤ 0.05.

Figure 2. ZIKV viremia is delayed and protracted and ZIKV viral burden more persistent in tissues in SIV-infected macaques

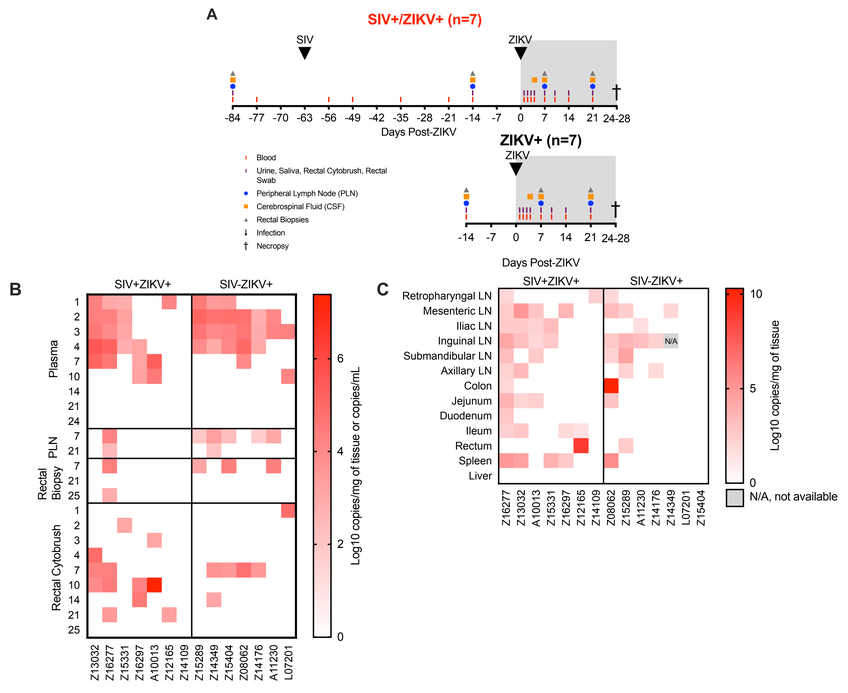


Figure 2. ZIKV viremia is delayed and protracted and ZIKV viral burden more persistent in tissues in SIV-infected macaques. (A) Study design of longitudinal blood and tissue sampling following SIV and ZIKV infections in pigtail macaques (n=7/group). (B) Quantitative real-time PCR (qRT-PCR) for ZIKV RNA in longitudinal samples from plasma, peripheral lymph node (PLN), rectal biopsies, and rectal cytobrush. (C) ZIKV RNA in tissues collected at necropsy 24-28 DPI.

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Figure 3. Recruitment of CD16+ monocytes and macrophages is dampened in the periphery but enhanced in tissues in SIV-infected macaques

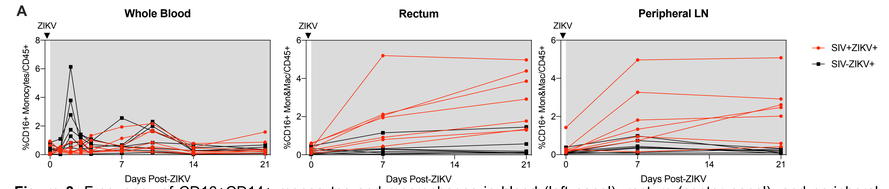


Figure 3. Frequency of CD16+CD14+ monocytes and macrophages in blood (left panel), rectum (center panel), and peripheral lymph node (right panel) after ZIKV infection.

Figure 4. SIV infection impairs anti-ZIKV immunity

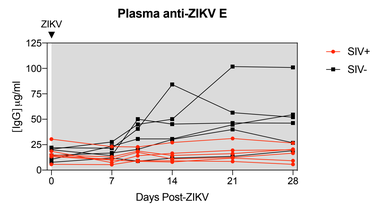


Figure 4. Longitudinal plasma concentrations of anti-ZIKV envelope (E) IgG as determined by ELISA (n=6/group).

Figure 5. Hyperactivation and sustained innate immune gene expression during SIV-ZIKV coinfection

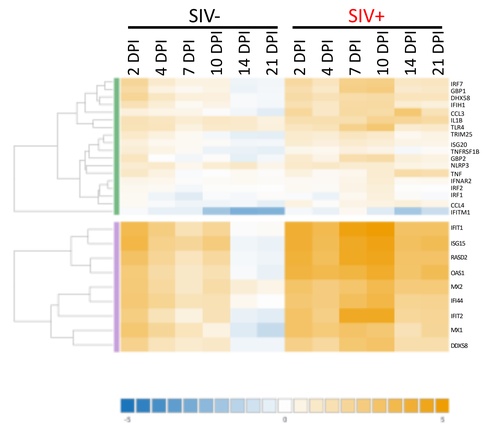


Figure 5. Heatmap showing 21 differentially expressed genes in at least one condition. Two clusters were defined using hierarchical clustering analysis. Differential gene expression between sample timepoints days post ZIKV infection (DPI) and days post ZIKV infection relative to respective baseline specimens (Group 1: (-63) DPI; Group 2: (-14) DPI). Orange represents increased gene expression relative to baseline. Gene expression of PBMCs was determined using a custom NanoString gene codeset and analyzed using Rosalind® meta-analysis.

Main Findings

- Prolonged ZIKV viral shedding during SIV infection may increase the window of ZIKV transmissibility
- Impaired cellular innate immune responses during SIV infection may impair early anti-viral responses needed for ZIKV viral clearance
- Chronic activation of innate signaling pathways during SIV-ZIKV coinfection may lead to viral tolerance

Key takeaway: Untreated SIV/HIV infection could create an environment of immunological tolerance that may lead to poor ZIKV viral clearance and promote pathogenesis.