Innate impairment during SIV infection alters ZIKV viral pathogenesis

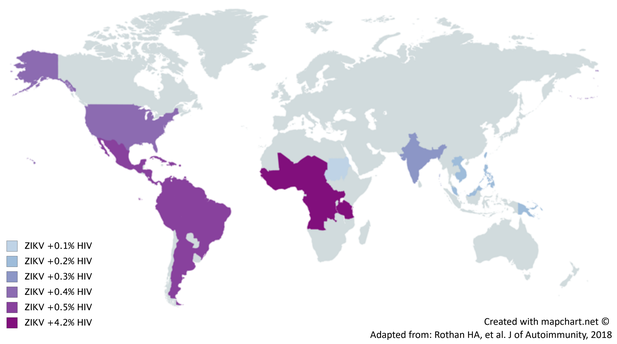
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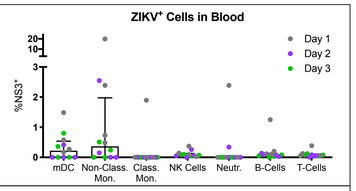
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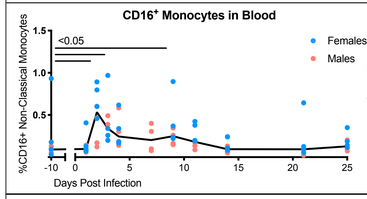
Background and Hypothesis

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 impact on co-morbidities.



CD16⁺ monocytes are major ZIKV blood cellular targets

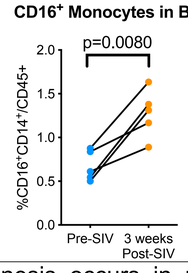




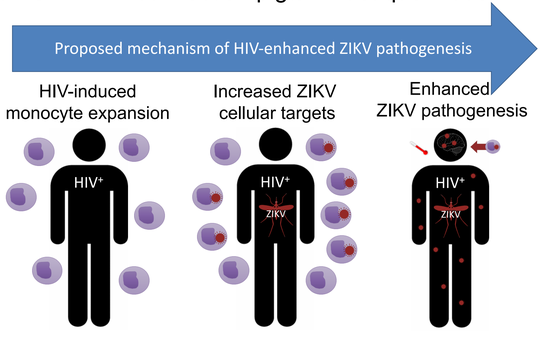
CD16⁺ monocytes expand during ZIKV infection in humans and non-human primates

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 model.



Results

Figure 1. Study Design: ZIKV coinfection in SIV-infected macaques

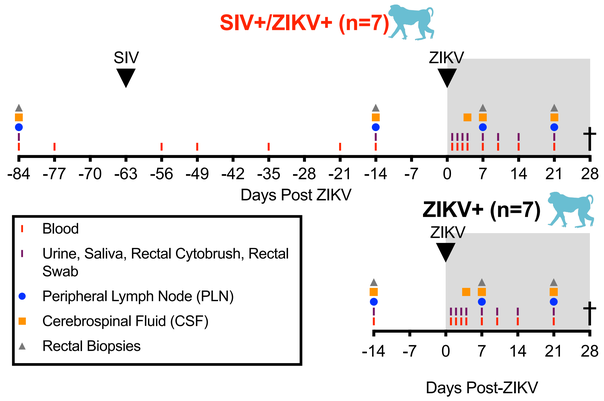


Figure 1. Pigtail macaques (PTMs) (n=7) were i.v. infected with SIVmac239M and coinfected with ZIKV at 9 weeks post-SIV. SIV infected (n=7) and naive animals (n=7) were subcutaneously (s.c.) infected with 5×10^5 plaque-forming units (PFU) of a Brazilian Fortaleza isolate of ZIKV.

Figure 2. SIV viremia and peripheral CD4 counts remain stable post-ZIKV coinfection

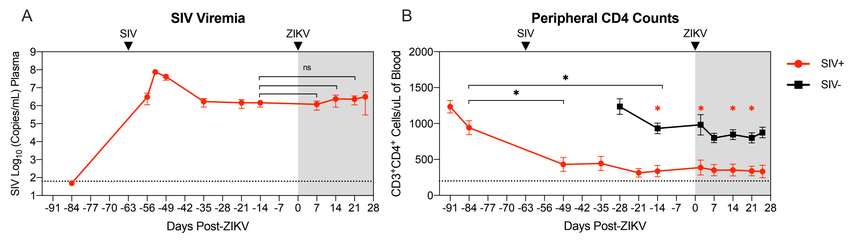


Figure 2. A. Viral load determined by qRT-PCR in plasma. B. CD4⁺ T-cells in the blood were quantified by complete blood count (CBC) using a hematology analyzer. A-B. Stats between timepoints: two-tailed Wilcoxon matched pair rank. Stats between experimental groups: T-test, adjusted for multiple comparisons.

Figure 3. Delay in peripheral ZIKV viral clearance during SIV infection

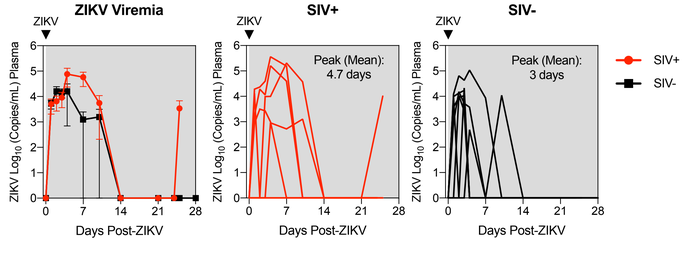


Figure 3. Kinetics of ZIKV RNA levels in the plasma (Log_{10} copies/ml) were determined by RT-qPCR. Mean ± SEM (left panel) and individual animals (middle and right panel) are indicated.

Figure 4. Delayed and dampened expansion of ZIKV cellular targets in blood corresponds with recruitment to tissues during SIV-ZIKV coinfection

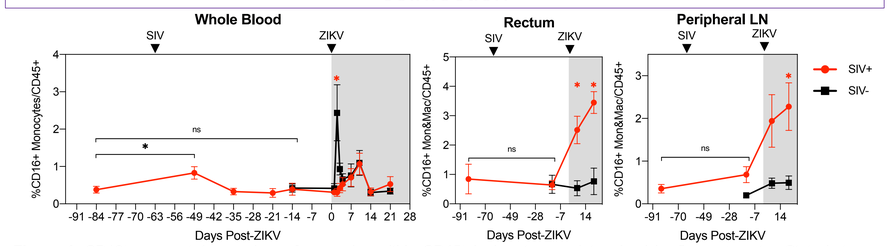


Figure 4. CD16⁺ monocyte/macrophage frequencies within CD45⁺ leukocytes as determined by flow cytometry. Stats between timepoints: two-tailed Wilcoxon matched pair rank. Stats between experimental groups: T-test, adjusted for multiple comparisons.

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

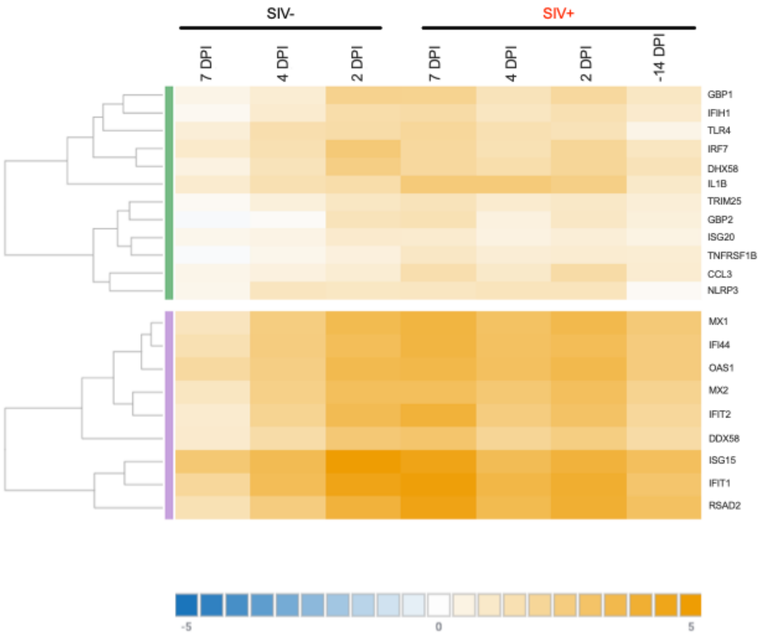


Figure 5. Heatmap showing 21 differentially expressed genes in at least one condition. Two clusters were defined using hierarchical clustering analysis. Differential gene expression between sample timepoints days post ZIKV infection (DPI) and days post ZIKV infection relative to respective baseline specimens (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.

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