DURABLE ART SUPPRESSION IN AGED RHESUS MACAQUES IS ASSOCIATED WITH MHC-I ALLELES

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Background

The advent of antiretroviral therapy (ART) has led to a remarkable increase in people who are aging with HIV infection. Indeed, an estimated 70% of people with HIV (PWH) in the USA in 2020 were over the age of 50. As these numbers are expected to rise over the next decade, it would suggest a marked increase in the overall prevalence of HIV amongst older populations. As such, there is growing need to understand how aging impacts the control of HIV replication and response to treatment. Aging is associated with the dysregulation of several components of the innate and adaptive immune systems. Cellular defects such as increased T cell turnover and shortening of telomeres, T cell exhaustion, change in CD4/CD8 ratios, expansion of terminally differentiated memory T cells (TM), decline in the naïve T cell (TN) pool and reduced B cell counts have all been reported. The disruption in TN homeostasis, in particular, can result in a decrease in TCR repertoire diversity that limits the ability of the host to protect against new or evolving pathogenic challenges. However, as observed with the recent COVID-19 pandemic, the immunological response in aged individuals can often be heterogenous with some data suggesting the ability to generate de novo T cell responses against acute and chronic viral infections is not universally impaired in the elderly (1-2). In this study, we used old (17-23 years) rhesus macaques (RM) stratified into 2 groups (n=8 each) based on protective (Mamu A*01, B*08 or B*17) or no known protective MHC-I alleles to determine how age-related immune impairments impact CD8+ T cell-mediated control of SIVmac239 replication and viral suppression following combination ART (cART) or during suboptimal treatment with tenofovir disoproxil fumarate (TDF) monotherapy.

References

1. *Lelic A., et al., 2012. The polyfunctionality of human memory CD8+ T cells elicited by acute and chronic virus infections is not influenced by age. PLoS Pathog, 8, p. e1003076.*
2. *Cicin-Sain L, et al. 2011. Cytomegalovirus-specific T cell immunity is maintained in immunosenescent rhesus macaques. J Immunol 187: 1722–1732.*

Aging alters T and B cell dynamics in RM

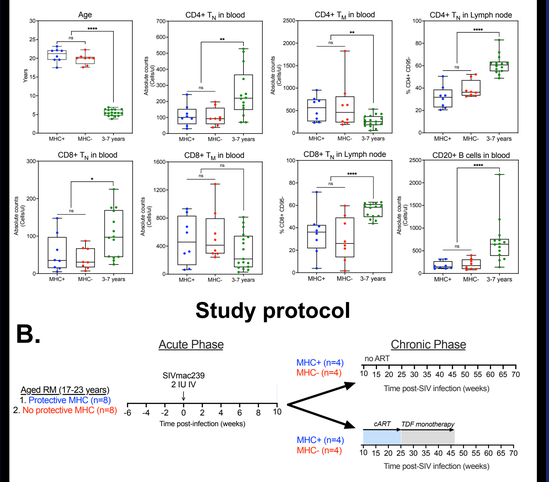


Figure 1: (**A**) Comparison of age, CD4+ and CD8+ naïve (TN) and memory T cell (TM) counts in blood and proportion of CD4+ and CD8+ TN in lymph node (LN) of old RM with RM protective MHC (n=8) or no protective MHC (n=8) versus young adults RM (n=17). (**B**) Schematic representation of the animal protocol that included IV inoculation of 2 IU of SIVmac239 and monitored for 10 weeks (acute phase). Subsequently, 8 old RM (+/- MHC) were started on cART consisting of dolutegravir, emtricitabine and tenofovir disoproxil fumarate (TDF) for 15 weeks followed by TDF monotherapy for a further 21 weeks prior to cART release (chronic phase). * p < 0.05, ** p < 0.005, **** p < 0.0001, ns = not significant.

Aged RM with protective MHC-I have lower plasma viral loads during acute infection

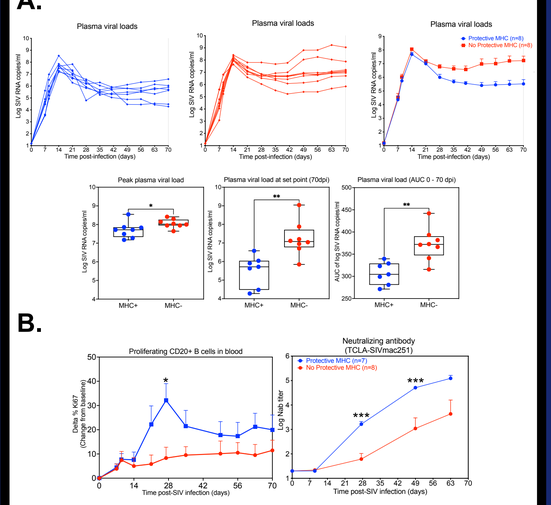


Figure 2: (**A**) Plasma viral load profiles of RM stratified by MHC+/MHC- group following challenge with SIVmac239. Comparison of mean (+/- SEM) PVL by age group. (Bottom Panel) Comparison of PVL at peak (day 14 pi), PVL at set point (day 70 pi) and PVL AUC (day 0-70 pi). (**B**) (Left). Results are shown as mean (+SEM) proliferative response Ki67+ CD20+ B cells. (right) Anti-ENV antibody titers by RM group. * p < 0.05, ** p < 0.005, *** p < 0.0005.

CD4+ T cell dynamics during acute SIV infection

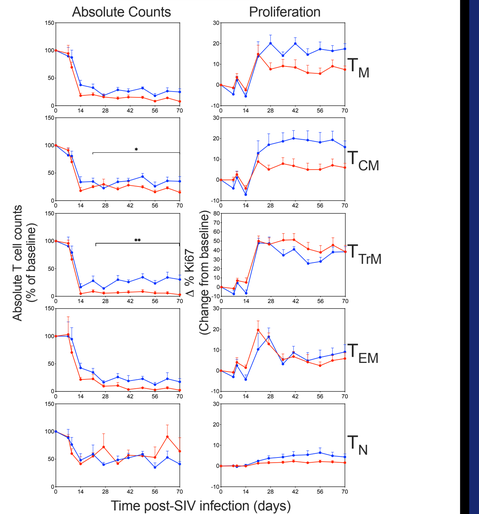


Figure 3: Mean (+ SEM) absolute counts (left panels) and change in proliferative fraction (right panels) of CD4+ T cell subsets in blood through 70 days post-infection (dpi). Total memory T cells (TM), central memory (TCM), transitional memory (TTrM), effector memory (TEM), naïve T cell (TN). * p < 0.05, ** p < 0.005 (AUC 21-70 dpi)

CD8+ T cell dynamics during acute SIV infection

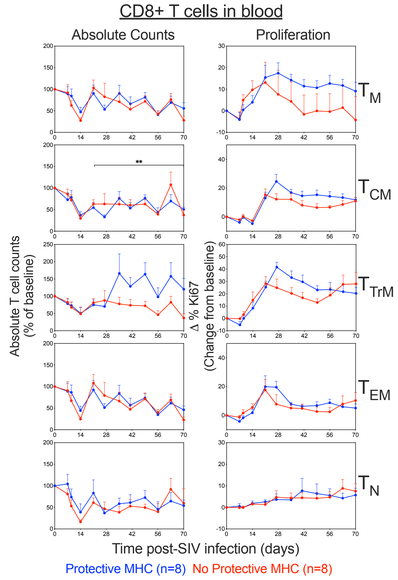
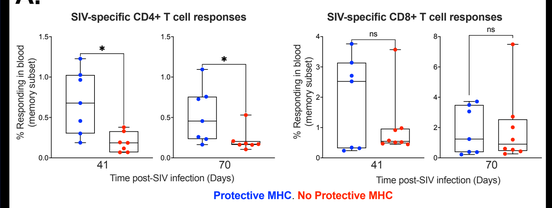


Figure 4: Mean (+ SEM) absolute counts (left panels) and change in proliferative fraction (right panels) of CD8+ T cell subsets in blood through 70 days post-infection (dpi). Total memory T cells (TM), central memory (TCM), transitional memory (TTrM), effector memory (TEM), naïve T cell TN. ** p < 0.005 (AUC 21-70 dpi)

Aged RM with protective MHC-I have higher SIV-specific CD4+ T cell responses



Aged RM with protective MHC-I maintain lower viral loads during chronic infection

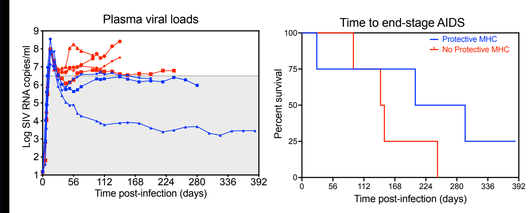


Figure 5: (**A**) Sum of CD4+ and CD8+ T cell responses in blood against SIV Gag, Nef and Pol at 41 and 70 days post-SIV infection (**B**). Plasma viral load profiles (left panel) and survival curve (right panel) of aged RM with protective MHC (n=4) or no protective MHC (n=4) alleles. * p < 0.05, ns = not significant.

Aged RM with protective MHC-I remain virally suppressed during ART and TDF monotherapy

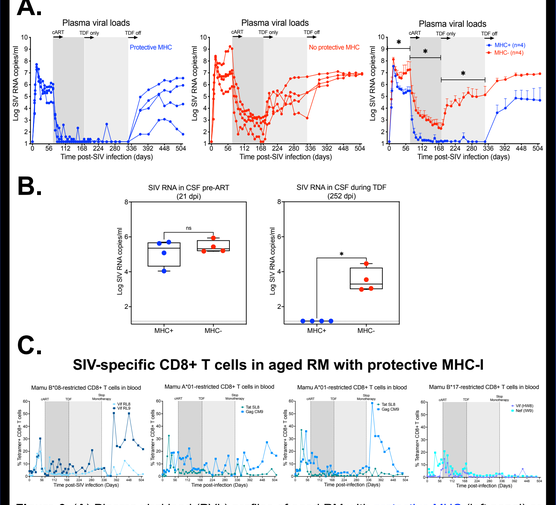


Figure 6: (**A**) Plasma viral load (PVL) profiles of aged RM with protective MHC (left panel) or no protective MHC (middle panel) and PVL mean (+SEM) (left panel) following challenge with SIVmac239, cART treatment at 70 days post-infection (dpi) followed by TDF monotherapy on 175 dpi. (**B**) SIV RNA in cerebrospinal fluid (CSF) on 21 dpi and during TDF monotherapy (252 dpi). (**C**) Frequencies of tetramer+ CD8+ cells in the 4 RM with protective MHC alleles. Mamu **A*01** (n=2 RM) Gag CM9, Tat SL8; **B*17** (n=1 RM): Nef IW9, Vif HW8; **B*08** (n=1 RM): Vif RL9 and Vif RL8. * p < 0.05, ns = not significant.

Summary

- Aging is associated with a marked decrease in CD4+ and CD8+ TN and CD20+ B cells in rhesus macaques (RM).
- During acute SIVmac239 infection, plasma viral loads (pvl) were significantly lower in aged RM with protective MHC-I alleles relative to aged RM with no protective MHC-I alleles.
- Aged RM with protective MHC-I alleles had improved anti-ENV responses and reduced CD4+ memory T cell depletion relative to aged RM with no protective MHC-I alleles.
- Aged RM with protective MHC-I alleles had a rapid decrease in pvl to below 15 RNA copies/ml during ART, and stringent viral suppression in plasma and cerebrospinal fluid was maintained during TDF monotherapy.
- In contrast, RM with no protective MHC alleles had delayed viral suppression in response to ART and rebound viremia following the switch to TDF monotherapy.
- Collectively, our results demonstrate that optimized CD8+ T cell responses can support virologic suppression in aged RM, even during suboptimal treatment.
- Enhancing HIV-specific CD8+ T cell immunity in people aging with HIV infection may be an effective strategy to improve treatment outcomes.

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