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Virologic and immunologic correlates of viral control post-ART interruption in SIV-infected rhesus macaques

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Background: Antiretroviral therapy (ART) does not eradicate HIV and the virus rebounds upon treatment interruption. Recently, a sustained control of HIV replication in the absence of ART has been achieved in a subset of patients starting ART early after infection, defined as post-ART treatment controllers (PTC). Unfortunately, the virologic and immunologic determinants of post-ART control of HIV replication are still unclear, particularly in tissues. Here, we used the well-established model of SIV-infection in rhesus macaques (RMs) to investigate the existence of PTC in this model and the features associated with post-ART SIV control.

Methods: 15 RMs (B*08- and B*17-) were infected (i.v.) with SIVmac239. All 15 animals initiated a 5-drug ART regimen 60 days after infection, which was maintained for seven months. ART was then interrupted and RMs monitored for eight additional months. Blood (PB), lymph node (LN), and colorectal (RB) biopsies were collected throughout the study. Quantitative assessment of total SIV-DNA and RNA was performed on purified blood CD4 T cells and mucosal tissues by quantitative PCR; immunological parameters were determined by flow cytometry.

Results: ART suppressed SIV-RNA to < 60 copies/mL in all RMs. After ART interruption, 6 RMs controlled SIV viremia at < 103 copies/mL up to 8 months off-ART (PTC), while 9 RMs rebounded to pre-ART levels (non-controllers, NC). At pre-ART, PTC had significantly lower plasma viremia and SIV-DNA content, as well as higher CD4 T cell counts as compared to NC. Levels of intestinal CD4 T cells were similar, but PTC had higher frequencies of Th17 cells than NC. On-ART, PTC had significantly lower levels of residual plasma viremia (3 copies/mL, limit of detection) and SIV-DNA content (both in blood and colorectum). After ART interruption, SIV-DNA content rapidly increased in NC while it progressively decreased in PTC. Finally, in PTC control of SIV rebound associated with higher CD4 T cell levels and reduced immune activation in PB and RB during the entire off-ART period.

Conclusions: Lower set point viremia, reduced cell-associated SIV-DNA, and preserved Th17 cell homeostasis associate with improved virologic response to ART and sustained viral control post-ART interruption in SIV-infected RMs.

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