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## RESTORATION OF MEMORY CD4<sup>+</sup> CCR5<sup>+</sup> T CELLS IN THE GASTROINTESTINAL TRACT DURING THE CHRONIC STAGE OF SIV INFECTION PREDICTS LONG-TERM NON-PROGRESSION

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**BACKGROUND:** Rapid and massive depletion of memory CD4<sup>+</sup>CCR5<sup>+</sup> cells in the gut-associated lymphoid tissue (GALT) in acute infection is a hallmark of HIV and simian immunodeficiency virus (SIV) pathogenesis. However, it is not known whether long-term non-progressors (LTNP) experience the same rapid and profound loss of gut CD4<sup>+</sup> cells in the acute infection. We have used LTNP SIV-infected rhesus macaques as a model to test the dynamics of memory CD4<sup>+</sup>CCR5<sup>+</sup> cells in GALT.

**METHODS:** We used 12 SIV-infected Chinese-origin rhesus macaques. Blood, lymph node, and intestinal biopsies were sampled before and post infection. CD8<sup>+</sup> cell depletion was performed using anti-CD8 monoclonal antibody in 2 of 4 LTNP. Expression of T cell, naïve and memory, activation and SIV co-receptor markers were measured by flow cytometry.

**RESULTS:** Of 12 monkeys, 8 developed AIDS between 6 and 25 months after infection (progressors); 4 were LTNP and remained healthy with undetectable plasma viral loads. Memory CD4<sup>+</sup>CCR5<sup>+</sup> cells were profoundly depleted at days 11 to 28 post infection in all 12 monkeys. The ability to restore memory CD4<sup>+</sup>CCR5<sup>+</sup> cells was defined as the percentage of these cells post infection, compared to baseline levels. In progressors, all lacked the ability to maintain restoration of memory CD4<sup>+</sup>CCR5<sup>+</sup> cells. In the LTNP, variable memory cell recovery began at day 60 post infection and all had restored 15% or more of baseline levels by day 180 and maintained this level or increased it. In 2 of 4 LTNP (AJ07 and V542), *in vivo* CD8<sup>+</sup> depletion was done to test the role of CD8 cells in LTNP on memory CCR5<sup>+</sup> cell restoration. AIDS was induced in 1 (V542) at day 35 post anti-CD8 treatment, the other (AJ07) remains healthy. Viremia returned but then declined. The rate of mucosal restoration of memory CD4<sup>+</sup>CCR5<sup>+</sup> cells was 1.8-fold faster in AJ07 than V542. Treatment with anti-CD8 monoclonal antibody greatly reduced gut CD8<sup>+</sup>

cells from 70% to 0.5% in AJ07 and from 60% to 0.1% in V542 at day 9. By day 35, AJ07 had restored CD8<sup>+</sup> cells to 79.9%, V542 had only 39.6%, suggesting that a rapid rate of CD8 cell recovery was necessary to return to the LTNP state.

**CONCLUSIONS:** Profound depletion of memory CD4<sup>+</sup>CCR5<sup>+</sup> cells in GALT was indistinguishable between disease progressors and LTNP at the acute stage of infection. Restoration of mucosal memory CD4<sup>+</sup>CCR5<sup>+</sup> cells during the chronic phase predicted LTNP. Sufficient CD8<sup>+</sup> T cells may be essential for controlling SIV infection in GALT and required for restoration of memory CD4<sup>+</sup>CCR5<sup>+</sup> T cells.

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