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Intestinal CX3CR1+Macrophage Dysregulation Drives Immune Activation and Viral Persistence in Chronic SIV Infection: Implications for HIV-1 Cure Strategies

Abstract: Chronic HIV-1 and SIV infections are characterized by persistent immune activation and inflammation, despite antiretroviral therapy (ART). This study explores the role of intestinal CX3CR1+ macrophages (MΦs) in immune dysregulation during chronic SIV infection and their impact on HIV-1 persistence after antiretroviral treatment interruption (ATI).

Using a cohort of Cynomolgus macaques, we analyzed mucosal CX3CR1+ MΦs and T cell subsets during chronic SIV infection and post-ATI. Results revealed an accumulation of pro-inflammatory MΦs in infected animals, with positive correlations to viral load. Post-treatment controllers (PTCs) showed restored MΦ homeostasis, suggesting a potential role in viral control after therapy interruption.

Additionally, chronic SIV infection led to significant shifts in mucosal T-cell populations. CD4+ T cells, especially Tregs, were depleted in the colonic mucosa of infected animals, with partial restoration observed in PTCs but not in non-controllers. Th1 CD4+ cells increased, while Th17 cells showed a trend towardreduction, correlating with the accumulation of pro-inflammatory MΦs. CD4+ T cells in infected and non-controller animals exhibited activation markers, including PD-1, HLA-DR, and Ki67. Activated neutrophils (CD66+CD32a+) also increased, correlating with pro- inflammatory MΦs and elevated fecal calprotectin, an indicator of intestinal damage.

These findings provide insights into the interplay between mucosal immune cell populations during chronic SIV infection, highlighting immune dysfunction and gut damage that may contribute to viral rebound post-ATI. Our study suggests that strategies to preserve or restore CX3CR1+ macrophage function are essential for advancing HIV cure research.

Keywords: HIV-1/SIV, immuneactivation, macrophages, post-treatment control

Biography: Dr. Mariangela Cavarelli, PhD, leads the “Intestinal Infection and Immunity” group and the “Serology technological platform” at IDMIT, CEA, France. Her research focuses on mucosal immune responses and transmission dynamics in infectious diseases, such as HIV/SIV, SARS-CoV-2, and Monkeypox. She contributes to developing prevention strategies and vaccines, with several key publications and collaborations in the field.

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