### Abstract

**Background:** Th17 cells are major players in mucosal immunity. Th17 cells are highly permissive to HIV infection, while Th1 cells are relatively resistant. As a consequence, Th17 are depleted in HIV-infected subjects and their frequency is partially restored under antiretroviral therapy. To identify molecular mechanisms of HIV permissiveness in Th17 cells, we performed a genome-wide analysis of gene expression in Th17 vs. Th1 cells.

**Methods:** Th17 (CCR4+CCR6+) and Th1 (CXCR3+CCR6-) subsets were sorted by flow cytometry and stimulated via CD3/CD28 Abs. The expression of 47,000 probe-sets was tested using the Illumina technology. Genes were classified by biological function using GO and GSEA. Real-time RT-PCR and fluorescence microscopy were used to validate differential gene expression. The RNA interference was used to evaluate the functional role of top-modulated genes. Cytokine production and proliferation was measured by flow cytometry. HIV infection was determined by HIV-p24 and integrated HIV-DNA.

**Results:** HIV permissiveness in Th17 vs. Th1 was regulated by both entry and post-entry mechanisms. Among 2,533 "present" genes, Th17 upregulated and downregulated, respectively, in Th17 vs Th1 cells. Genes associated with T-cell differentiation (RORC), TCR signaling (ZAP70, Lck, MAP3K4), activation/apoptosis (PTPN13), and HIV replication (PPARG) were upregulated in Th17 vs. Th1 cells. Genes downregulated in Th17 vs. Th1 cells and previously linked to HIV resistance included CCR5-binding chemokines and IFN-induced molecules. HIV permissiveness in Th17 vs. Th1 cells was associated with high sensitivity to TCR triggering, increased proliferation potential, and superior NF-κB DNA-binding activity. RORC RNA interference decreased HIV replication, while PPARG silencing induced opposite effects.

**Conclusion:** Our study reveals a unique molecular signature in HIV-permissive Th17 and identifies RORC and PPARG as two major regulators of HIV replication in these cells. Finding strategies to limit HIV replication in Th17 cells, while preserving their polarization profile and beneficial role in mucosal immunity, remains a challenge for the future.

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