HIV-1 controllers (including post-treatment controllers)

PE21

Profound alterations in cholesterol metabolism restrict HIV-1 trans infection of CD4 T-cells in nonprogressors

Rappocciolo G., Martinson J., Piazza P., Gupta P., Rinaldo C.R.

University of Pittsburgh, IDM, Pittsburgh, United States

Background: The small percentage of HIV-infected individuals who control HIV disease progression for many years without cART (NP - nonprogressors) offer a natural model of viral control and clues to curing the infection as well as developing therapeutic and prophylactic vaccines. We have reported that professional antigen-presenting cells (APC), i.e., dendritic cells (DC) and B cells, from HIV-1 infected NP are inefficient in trans infection of T cells due to altered cholesterol metabolism, potentially reducing spread of virus and controlling disease progression. Importantly, APC from NP showed impaired trans infection both prior to and after primary HIV-1 infection, whereas APC from progressors had this capacity both before and after infection, supporting a host genetic basis for this impairment.

Methods: We conducted a whole genome transcription analysis on DC, B cells and CD4+ T cells from NP and PR to identify differential expression of genes related to cholesterol metabolism. RNA was isolated from APC derived from NP and PR (progressors) and microarray analysis of mRNA transcripts was performed on Illumina HT12.

Results: NP overexpressed genes related to cholesterol metabolism pathways compared to PR. In DC peroxisome proliferator-activated receptor gamma (PPAR-γ) involved in the upregulation of ABCA1 and CD36 receptor for oxidized LDL, and in B cells, genes related to the endocytosis of LDL and the LDL receptor (LDLR), as well LXRα, which up regulates ABCA1 activity upon trans activation by its natural ligands, such as oxysterols. The higher levels of transcripts for these genes were confirmed by RT-PCR.

Conclusions: We have shown that APC from NP completely lack the ability to trans infect T cells. This was associated with profoundly enhanced cholesterol metabolism that appears to be an inherited trait, and we have identified gene(s) involved in the uptake, trafficking and metabolism of cholesterol that are associated with the phenotype of defective trans infection. These results provide a basis for therapeutic interventions to control of HIV-1 infection through modulation of cholesterol metabolism.