Targeting IFN-I signaling during persistent HIV-1 infection enhances memory CD4 T-cell survival through AKT activation (Julien van Grevenynghe; IAF-INRS)

Abstract

In addition to metabolic disturbances, modern antiretroviral therapy (ART) is unable to counteract immune defects that are associated with residual inflammation alongside viral persistence. To eventually achieve ART termination, it is critical to find new ways to boost protective immunity which include the restoration of long-lasting memory CD4 T-cells (Mem) in HIV-1-infected patients. Herein, we show that Mem from infected subjects, even in patients under ART, display sustained type I interferon (IFN-I) signaling that can be reversibly normalized using a monoclonal antibody to block $IFN_{\alpha/\beta}$ receptor (IFNAR) pathway. Our data report that IFNAR blockade during HIV-1 infection not only improves Mem response to IL-2 and IL-7 cytokines, but also enhances cell protection against Fas-induced apoptosis. We find that targeting IFN-I signaling in Mem from infected patients allows them to persist longer after multiple rounds of T-cell receptor triggering. Finally, our data indicate that improvements of Mem survival upon IFNAR blockade are driven by increased AKT activation levels.

Our study findings indicate that **blocking IFNAR during HIV-1 infection may provide a potential strategy to enhance Mem recovery and long-term survival, even in patients with early initiation of ART.**