Impairment of CD1d-Restricted Natural Killer T Cells in Chronic HIV Type 1 Clade C Infection

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Abstract

Recent studies suggest that natural killer T (NKT) cells play a role in early antiviral pathogenesis and are rapidly depleted in chronic human immunodeficiency virus type 1 (HIV-1) clade B infection. We aimed to characterize the phenotypic and functional characteristics of NKT cells in HIV-1 clade C-infected Africans at different stages of HIV-1 disease. NKT cell frequencies, subsets, and ex vivo effector functions were assessed using multi-parametric flow cytometry in a cross-sectional analysis of cryopreserved peripheral blood mononuclear cells from a cohort of 53 HIV-1 clade C chronically infected South African adults with CD4 T cell counts ranging from 94 to 839 cells/μl. We observed a significant decline of NKT cell numbers in advanced HIV-1 disease as well as activation and functional impairment of NKT cells in individuals with low CD4 T cell counts. The loss of NKT cells was largely driven by a reduction in the CD4+ and CD4–CD8– NKT cell subsets in advanced disease. These findings demonstrate significant impairment of the NKT cell compartment in progressive HIV-1 clade C disease that might play an important role in the modulation of immune function in HIV-1 infection.

Introduction

Natural killer T (NKT) cells are a distinct population of CD3+ T cells that recognize glycolipid antigens presented by the MHC class-I-related glycoprotein CD1d1,2 and express nearly invariant T cell receptors.3 NKT cells are rapid immune responders and mediate potent immunoregulatory and effector functions.4 Once activated, NKT cells are cytolytic and produce high levels of cytokines such as interferon (IFN)γ, interleukin (IL)-4, and IL-175 that can subsequently activate dendritic cells, natural killer (NK) cells, and CD4 and CD8 T cells.6,7 Several viruses such as herpes simplex and influenza viruses have developed immune-invasion strategies that impair CD1d-mediated antigen presentation8,9 suggesting that NKT cells may play a key role in antiviral immunity. The precise role of NKT cells in HIV-1/SIV infection is not well understood, however, several studies have shown a reduced frequency of circulating NKT cells in chronic infection.10-12 Furthermore, it has been reported that initiation of highly active antiretroviral therapy (HAART) in conjunction with IL-2 treatment can result in rapid recovery of circulating subsets of NKT cells.13,14 Interestingly, HIV-1 Nef can mediate downregulation of CD1d expression by increasing CD1 internalization.15,16 In addition, HIV-1 Vpu promotes evasion from CD1d-restricted immunity by inhibiting cell surface expression of CD1d and consequently the activation of NKT cells suggestive that HIV-1 might have developed strategies to evade NKT-mediated immunity. These NKT cell studies have been largely performed in HIV-1 clade B-infected white populations, and very little is known about the impact of HIV-1 infection on overall NKT cell frequencies and function in sub-Saharan Africa where HIV-1 clade C is the most predominant subtype18 and where genetic factors and co-morbidities influencing antiviral immunity may differ from white populations.

In the current study, undertaken in a chronically HIV-1 clade C-infected adult cohort from KwaZulu-Natal, South Africa, we characterized the phenotypic and functional characteristics of NKT cells at different stages of HIV-1 disease.

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