Correspondence

Vγ2Vδ2 T Cells are Skewed Toward a Terminal Differentiation Phenotype in Untreated HIV Infection

To the Editor—With great interest we read the recent study by Boudová et al [1] who investigated the impact of chronic human immunodeficiency virus (HIV) infection on the frequency and differentiation status of CD4 Vγ2Vδ2 T cells in peripheral blood of patients from an African American cohort with a focus on patients with slow disease progression and low viral loads. These patients were termed “persistently viremic” (PV) by the authors, which is a less stringent definition of the more commonly used phrase “long-term nonprogressors” [2]. Boudová et al describe in this study how Vγ2Vδ2 cells are severely altered with regard to memory phenotype and expression of the cytotoxicity marker CD56 in HIV-infected patients [1].

We performed a similar analysis in a cohort consisting predominantly of white individuals, classified as healthy donors (HDs), antiretroviral therapy (ART)-treated HIV patients (HAARTs), and elite controllers (ECs), as shown in Figure 1A. In addition, we added a group of PV HIV patients, according to the definition of Boudová et al [1] for reasons of direct comparability, as well as patients with a viral load >100 000 copies/mL (HV) who were not included in the previous report [1]. Written informed consent was obtained from all patients and the study was approved by the local ethics committee. Vγ2Vδ2 T cells were defined as CD3+TCRgd+Vδ2+ lymphocytes, as shown in Figure 1B. All samples were run on an LSR II flow cytometer (BD) and analyzed with FlowJo Version 9 diagnostic software.

We also found alterations in the CD4 Vγ2Vδ2 T cell compartment in HIV patients, albeit with noteworthy differences. In agreement with a previous report [3], there was a trend toward a decreased frequency of Vγ2Vδ2 T cells among lymphocytes from HIV-infected individuals compared to HDs (Figure 1C). However, in our viremic (HV and PV) patients, but not in HAARTs or in ECs, we saw a significant skewing of the Vγ2Vδ2 subset toward an activated (CD38+Ki67+, data not shown) and terminally differentiated (CCR5−/CD28−) effector phenotype compared to HDs (Figure 1D). This is in stark contrast to the results of Boudová et al, who describe a trend toward a decline of the proportion of T effector memory (CD27−CD45RA−) cells in the Vγ2Vδ2 T cell compartment in all HIV-positive groups. We confirmed our results by additional memory marker staining for CD27−CD28− cells (data not shown). In general, accumulations of terminally differentiated and activated/exhausted T cells are regarded as a hallmark of the chronic progressive phase of HIV/simian immunodeficiency virus (SIV) infection [4], and are probably partially due to general immune activation [5] that is fueled by microbial translocation [2]. In agreement with our results for HIV-infected patients, Harris et al observed a decrease in the percentage of circulating less differentiated CCR5+/CD28+ Vγ2Vδ2 T cells in SIV-infected rhesus macaques [6].

Moreover, in our analysis, there is a trend toward a higher percentage of CD56+Vγ2Vδ2 T cells in HIV-infected individuals that reaches statistical significance for our HV patients (P < 0.001 for HD vs HV) (Figure 1E), whereas Boudová et al, surprisingly, find the proportion of these cytotoxic precursor cells to be decreased in all HIV-positive groups with the exception of the natural virus suppressor (NVS) group. Further studies should investigate the reasons for the differences seen in both studies before an active role in viral control for these cells in NVS groups can be postulated [1].

Among the possible reasons for the discrepant results are the different gating strategies or differences in the composition of the cohorts and blurry definition of patient subgroups (eg, the PV group). Importantly, as Boudová et al point out, baseline levels of Vγ2Vδ2 T cells are substantially lower for HIV-negative African Americans, compared with those in whites [7], and decline with age [8]. The fraction of CD56+ Vγ2Vδ2 cells is also significantly lower for African American donors than for white donors [7]. Our findings could suggest that not only baseline levels, but also HIV-induced alterations, of Vγ2Vδ2 T cells are different in patients from African and white descent, and raise questions regarding the underlying genetic determinants for this discordance.

In summary, we caution on generalization of the results by Boudová et al that are focused on a small subgroup of cells and patients [1]. Rather, further extended and comprehensive phenotypic and functional studies of the different γδ T cell subtypes are needed to compare patient cohorts of different ethnic background and disease status (including the distribution in different tissues) to fully comprehend the role of these cells in HIV pathogenesis. Only then will we have the basis to plan further immunomodulatory trials with these cells [1].
Figure 1. Alterations in the Vγ2Vδ2 T cell compartment in HIV patients from a white HIV cohort. A, Cohort characteristics. B, Gating strategy. Peripheral blood mononuclear cells were stained with a live-dead marker (Aqua, Invitrogen) and antibody panels that included the following antibodies: CD3-APC-H7, CD56-PE-Cy5, TCR-γδ-PE (BD), δ2-FITC (Beckman Coulter), CD4-BV421, CD27-Alexa fluoro-700, CD28-Paci fi c Blue, CCR5-PerCP-Cy5.5, CD38-APC, Ki67-PE-Cy7 (Biolegend). C, Frequency of Vδ2+ cells as percentage among CD3+ lymphocytes. D, Frequency of terminally differentiated effector T cells as percentage of CCR5-/CD28- cells among Vδ2+ T cells. E, Percentage of CD56+ cells among CD4 Vγ2Vδ2 T cells. One data point for EC lies outside of the axis limits (99%). Abbreviations: EC, elite controller; HAART, antiretroviral therapy–treated HIV patient, HD, healthy donor; HIV, human immunodeficiency virus; HV, patients with a viral load >100 000 copies/mL; PV, persistently viremic; VL, viral load.
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