Persistent Decreases in Blood Plasmacytoid Dendritic Cell Number and Function Despite Effective Highly Active Antiretroviral Therapy and Increased Blood Myeloid Dendritic Cells in HIV-Infected Individuals

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Dendritic cells (DC) have an instrumental role in the activation and function of both innate and adaptive immune responses. In humans, at least two distinct DC subsets have been characterized based on phenotypic markers: the myeloid DC (MDC) and the plasmacytoid DC (PDC). Both subsets are critical producers of cytokines (IL-12 for MDC and type I/II IFNs for PDC) and are functionally different. We show in this study that HIV+ individuals have a significant decrease in the number of the Lin−HLA-DR−CD123+ and BDCA-2−PDC compared with uninfected donors (p = 0.0001). HIV+ individuals also have a sustained impairment in viral-induced IFN-α production (p < 0.0001). The decrease of the PDC subsets did not correlate with CD4 count or viral load and was not reversed in subjects under virally suppressive treatment, suggesting an irreversible change after infection. By contrast, the absolute number and median frequency of MDC in HIV-infected individuals were similar to those observed in uninfected controls, while a significant decrease was present in subjects with >5000 HIV-1 copies/ml. The inverse association with viral load of the MDC number, but not of IFN-α secretion or the number of PDC, suggests a role for MDC in viral control. Our data suggest that DC subsets are differentially reconstituted during the immune recovery associated with antiviral therapy. The persistent impairment of certain DC subsets may result in a sustained defect in DC-mediated innate immune functions despite an effective treatment regimen. The Journal of Immunology, 2002, 168: 4796–4801.

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activity (22), and more recently a moderate increase in PDC after HAART (19). However, it remains unknown whether DC functions may be recovered following suppressive HAART and whether the MDC and PDC subsets are differentially regulated and associated with viral control in chronically HIV-infected subjects. The recent availability of new DC markers for MDC and PDC subsets (23) allows a more accurate detection, quantitation, and characterization of DC subsets in HIV infection.

To analyze the potential alteration in DC function in circulating blood during HIV infection, we evaluated phenotypic and biological properties of two major subsets of DC from a cross-sectional cohort of HIV-infected donors and uninfected control subjects. Our data show that MDC number is inversely associated with viral load in untreated chronic HIV-1-infected patients and increases under HAART, in contrast to a sustained loss of PDC (CD123+ or BDCA-2+) subset and a concurrent decrease in IFN-α secretion.

Materials and Methods

Patients and PBMC isolation

Consenting chronically HIV-seropositive patients (n = 65) at various stages of disease were enrolled in this study. All patients were from the Jonathan Lax Immune Disorder Clinic (Philadelphia Field Initiation Group for HIV Trials). CD4 T cell counts range from 9 to 1,347 (mean of 501 cells/mm3), and viral load from <50 to 199,000 copies/ml (mean of 15,091 copies/ml). Twenty-one patients were not receiving therapy, and 44 were under HAART. Ninety-six percent of virally suppressed patients (viral load <50 copies/ml) were under HAART. None of the patients presented any OI or HIV-related neoplasms. Healthy HIV-1-seronegative donors from non-HIV-1-infected donors and cord blood of healthy term neonates by Ficoll-Paque density gradient centrifugation was used as responders. Responding cells were cultured in triplicate for 5 days with 1 × 105 PFU HSV-1-NS for 18 h. As control for Influenza-PR8, allantoid fluid was used and did not induce any detectable amount of IFN-α (data not shown). Cell-free supernatants were harvested and tested by a commercial ELISA using matched Ab pair for IFN-α and performed according to the manufacturer (Endogen, Woburn, MA). Absorbance was measured on an automatic ELISA reader. Sensitivity of the assay was ~8–12 pg/ml.

Mixed lymphocyte reaction

MLR was performed as described by Young and Steinman (24). A total of 2 × 105 plastic nonadherent mononuclear cells isolated from the umbilical cord blood of healthy term neonates by Ficoll-Paque density gradient centrifugation was used as responders. Responding cells were cultured in triplicate for 5 days with 1 × 105/ml irradiated allogeneic stimulator cells in 96-well plates in 200 μl medium. Cultures were pulsed with [3H]Tdr (1 μCi/well; Amersham, Arlington Heights, IL) for 16 h. Nuclei were collected into fiberglass filter paper (Packard Instrument, Meriden, CT). Radioactivity in the filter paper was quantified as cpm by use of a direct beta counter 9600 (Packard Instrument). Results were expressed as stimulation index (SI) determined as follows: mean cpm in cultures containing responding and stimulator cells/mean cpm in culture containing responder cells alone. A SI of 3 and above was considered positive.

Statistical analysis

This was performed with JMP 4.0 software (SAS Institute, Cary, NC). Data were compared using paired or unpaired nonparametric tests, as appropriate. Statistical significance between HIV+ and HIV− was performed by the Wilcoxon tests. Correlation and association between CD4 counts, viral load, and other parameters were performed by the Spearman’s rank test. When indicated, the absolute number of leukocytes was determined by an automated differential blood count.

Results and Discussion

PDC and MDC subsets in HIV infection

We analyzed the phenotype and functions of the two major peripheral blood DC subsets (MDC and PDC) in a cross-sectional cohort of healthy uninfected controls (n = 53) and chronically

![FIGURE 1. Representative phenotypic analysis of MDC and PDC subsets. Whole blood (200 μl) assay is used. Multicolor staining for MDC (Lin− HLA-DR− CD11c+) and for PDC (Lin− HLA-DR− CD123+; HLA-DR+ BDCA-2+) is shown. After excluding dead cells based on light scatter gating, 150,000–200,000 events were acquired. A, PBMC from HIV− and HIV+ donors gated on HLA-DRhigh, and of Lin−, DC are identified based on CD123 (PDC) or CD11c (MDC) expression. B, The same donors stained with HLA-DR and BDCA-2.](http://www.jimmunol.org/)

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HIV-infected individuals (n = 65). Cells were quantified by multiparametric flow cytometry on whole blood (Fig. 1 shows a representative analysis). Our patient cohort consisted of HAART-treated (n = 44) and untreated individuals (n = 21), with a CD4+ T cell number ranging from 9 to 1,347/mm³ and a viral load from <50 to 199,000 copies/ml. The median frequency of PDC in control individuals was 0.29% (7,250 cells/ml). PDC were significantly (p < 0.001) decreased in patients (0.10%, 3,288 CD123+/H11001 cells/ml vs 0.07%, 1,750 cells/ml, p = 0.007, 8,250 cells/ml) for BDCA-2 subset as compared with healthy controls (Fig. 2 and Table I). The proportions of PDC (CD123+/H11001 and BDCA-2+) were highly correlated in both control (r = 0.55, p = 0.007, n = 21) and HIV-infected subjects (r = 0.64, p < 0.001, n = 33), indicating that these two phenotypes (CD123+/H11001 and BDCA-2+) identify largely overlapping cell subsets. Unlike PDC, the median frequency of MDC in HIV-infected patients (0.27%, 6,100 cells/ml) was similar to that observed in uninfected controls (0.27%, 6,625 cells/ml; Fig. 2 and Table I). Additional DC subsets analyzed include the newly described BDCA-3+ subset (23), which was found to be decreased in patients as compared with uninfected controls (0.03%, 1,000 cells/ml vs 0.07%, 1,750 cells/ml, p = 0.0034, data not shown). However, because the nature of the BDCA-3+ subset is still poorly understood, further functional characterization of this subset is needed before its role in the context of an immune response can be interpreted.

**IFN-α secretion and MLR response as functional correlates of PDC and MDC subsets**

To gain further insight into the functional outcome of the decrease in circulating PDC, we evaluated the production of IFN-α by healthy uninfected controls (n = 36) and HIV-infected individuals (n = 48) in response to Influenza-PR8 or HSV-1-NS strain exposure. IFN-α has a potent antiviral and antitumor activity and, within peripheral blood, it is selectively produced by PDC following enveloped viral stimulation (7, 11, 20). Consistent with a decreased number of circulating PDC in HIV infection, PBMC from HIV-infected patients produced on average 20-fold less IFN-α than PBMC from control donors when stimulated in vitro with either Influenza-PR8 or HSV-1-NS (p < 0.0001, Fig. 3). Moreover, a positive correlation was found between PDC frequencies and IFN-α production by PBMC in response to either virus (Rho = 0.8, p < 0.0001 for CD123, and Rho = 0.699, p < 0.0001 for BDCA-2, respectively).

We analyzed whether in HIV-infected patients APC-specific activities associated with MDC were affected by testing the ability of PBMC to stimulate proliferation of allogeneic T cells. We compared in PBMC from 14 HIV-infected patients and in 8 healthy controls the number of both DC subsets by phenotypical analysis and their associated functional properties. As shown in Table II, even though the PDC compartment was impaired in the HIV-infected patients (as indicated by their decreased frequency and IFN-α secretion), MDC frequency and the allostimulatory function of PBMC from the patients were comparable with those of the

### Table I. Characterization of DC subsets in peripheral blood of HIV-infected individuals

<table>
<thead>
<tr>
<th>DC Subsets</th>
<th>HIV+</th>
<th>HIV+</th>
<th>p Values&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC</td>
<td>0.27 (0.17–0.47)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.27 (0.13–0.40)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td>PDC (CD123&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>0.29 (0.13–0.42)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10 (0.05–0.18)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC (BDCA-2&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>0.37 (0.15–0.50)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.09 (0.05–0.14)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values represent percentage of positive cells and are expressed as median (25th–75th percentile).

<sup>b</sup> Statistical significance between HIV<sup>+</sup> and HIV<sup>+</sup>.

<sup>c</sup> n = 53 donors tested.

<sup>d</sup> n = 65 donors tested.

<sup>e</sup> n = 21 donors tested.

<sup>f</sup> n = 33 donors tested.
controls. Moreover, no significant difference was observed in the MLR assays between virally suppressed (<50 copies/ml) and viremic patients (>50 copies/ml). Our results, indicating that MDC from HIV-infected patients are not impaired in their ability to stimulate allogeneic T cells, are in agreement with earlier reports (25, 26) and with our previous observation using enriched population of total DC (27). Interestingly, we found a positive correlation between the frequency of the MDC subset and the MLR response (r = 0.70, p = 0.0073) consistent with a role for the MDC subset in this functional response. Taken together, these results strongly suggest a dichotomy between PDC and MDC in our cohort of HIV-infected individuals: the depletion of PDC is associated with impairment of IFN-α production, while MDC are maintained and retain functional allogeneic responses.

Lack of correlation between CD4 counts, viral load, and PDC number

We compared patients grouped according to CD4 count or viral load, as described in Materials and Methods, to address the question of whether the PDC and MDC subsets were affected by CD4 T cell counts, viral load, or antiretroviral therapy. Statistical analysis revealed no correlation between CD4 T cell counts or viral load and PDC frequency (defined by expression of CD123 + or BDCA-2 +), albeit their number in the patients was significantly decreased in comparison with healthy uninfected controls. Importantly, analysis of PDC in virally suppressed patients as compared with uninfected controls revealed a sustained decrease in both cell frequency and IFN-α secretion (Tables II and III), indicating that the loss of PDC is not reversed by antiretroviral treatment. IFN-α production was significantly associated with CD4 counts only when the analysis was restricted to viremic patients with >50 HIV copies/ml (data not shown). In contrast to a recent report in which increased levels of IFN-α secretion were described following HAART (28), impaired IFN-α production was observed in treated patients with complete viral suppression (<50 copies/ml) as well as in patients with persistent viral replication (>50 copies/ml, p < 0.0001 when compared with controls; Table III). The differences in the results reported in this study and the one mentioned above (28) could depend on specific characteristics of the patient cohorts studied: e.g., none of the patients used in this study had a history of O.I. or oncological diseases. It should also be noted that our interpretation of a sustained decrease in IFN-α secretion (by ELISA) rests on a direct comparison with uninfected controls, while the above mentioned study addressed recovery based on investigator-assigned thresholds of IFN-α secretion (by bioassay) within specific HIV + populations (28). Taken together, our results suggest that a loss of PDC may be an early event in HIV infection with a limited capacity for reconstitution following antiretroviral therapy, as reflected by persistent low frequency of PDC in subjects under treatment with <50 HIV copies/ml and high CD4 T cell count.

Although the exact mechanism responsible for the PDC deficiency remains to be defined, our observations argue against a predominant role of PDC in the control of HIV replication in chronic infection, as proposed by others (20, 21, 28). Of interest, we noticed that six of the HIV-infected subjects on HAART had PDC frequencies in the normal range (≥0.29%) and only two of these individuals, with CD4 counts

Table II. Differential functional responses of MDC and PDC in HIV-infected individuals

<table>
<thead>
<tr>
<th>Patients</th>
<th>MDC</th>
<th>PDC</th>
<th>Influenza IFN-α</th>
<th>HSV-1 IFN-α</th>
<th>MLR SI</th>
<th>CD4 T Cells/mm²</th>
<th>Viral Load (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P183</td>
<td>0.31</td>
<td>0.12</td>
<td>117</td>
<td>98</td>
<td>8</td>
<td>220</td>
<td>50</td>
</tr>
<tr>
<td>P187</td>
<td>0.55</td>
<td>0.25</td>
<td>388</td>
<td>497</td>
<td>11.4</td>
<td>388</td>
<td>50</td>
</tr>
<tr>
<td>P269</td>
<td>0.31</td>
<td>0.11</td>
<td>202</td>
<td>139</td>
<td>11.8</td>
<td>622</td>
<td>50</td>
</tr>
<tr>
<td>P271</td>
<td>0.31</td>
<td>0.11</td>
<td>309</td>
<td>201</td>
<td>9.6</td>
<td>188</td>
<td>50</td>
</tr>
<tr>
<td>P272</td>
<td>0.19</td>
<td>0.17</td>
<td>498</td>
<td>218</td>
<td>10.4</td>
<td>598</td>
<td>50</td>
</tr>
<tr>
<td>P273</td>
<td>0.31</td>
<td>0.15</td>
<td>189</td>
<td>189</td>
<td>11.8</td>
<td>459</td>
<td>50</td>
</tr>
<tr>
<td>P275</td>
<td>0.29</td>
<td>0.17</td>
<td>375</td>
<td>218</td>
<td>10.4</td>
<td>598</td>
<td>50</td>
</tr>
<tr>
<td>P276</td>
<td>0.21</td>
<td>0.12</td>
<td>87</td>
<td>87</td>
<td>7.6</td>
<td>175</td>
<td>73</td>
</tr>
<tr>
<td>P277</td>
<td>0.14</td>
<td>0.12</td>
<td>209</td>
<td>209</td>
<td>9</td>
<td>283</td>
<td>112</td>
</tr>
<tr>
<td>P278</td>
<td>0.44</td>
<td>0.18</td>
<td>178</td>
<td>221</td>
<td>12.6</td>
<td>340</td>
<td>132</td>
</tr>
<tr>
<td>P185</td>
<td>0.26</td>
<td>0.09</td>
<td>90</td>
<td>ND</td>
<td>9.6</td>
<td>289</td>
<td>2,480</td>
</tr>
<tr>
<td>P276</td>
<td>0.41</td>
<td>0.19</td>
<td>312</td>
<td>234</td>
<td>10</td>
<td>1,050</td>
<td>7,150</td>
</tr>
<tr>
<td>P184</td>
<td>0.09</td>
<td>0.2</td>
<td>89</td>
<td>220</td>
<td>2.5</td>
<td>313</td>
<td>28,300</td>
</tr>
<tr>
<td>P186</td>
<td>0.22</td>
<td>0.19</td>
<td>289</td>
<td>401</td>
<td>7</td>
<td>600</td>
<td>48,600</td>
</tr>
<tr>
<td>All patients (n = 14)</td>
<td>0.29 ± 0.03</td>
<td>0.16 ± 0.013</td>
<td>217 ± 29</td>
<td>221 ± 31</td>
<td>9.5 ± 0.7</td>
<td>401 ± 67</td>
<td>6,228 ± 3,835</td>
</tr>
<tr>
<td>All controls (n = 8)</td>
<td>0.30 ± 0.035</td>
<td>0.32 ± 0.03</td>
<td>1,459 ± 370</td>
<td>1,113 ± 306</td>
<td>9.22 ± 0.6</td>
<td>p values&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Results represent percentage of positive cells ± SE. PDC are defined by HLA-DR + CD123 +/BDCA-2 +. Viral stimulated IFN-α measured in picograms per milliliter ± SE. Statistical significance between HIV + and HIV − was performed using the Wilcoxon test.

Table III. DC subsets and viral load in HIV-infected individuals<sup>b</sup>

<table>
<thead>
<tr>
<th>DC Subsets/IFN-α</th>
<th>HIV (&lt;50 copies/ml)</th>
<th>HIV (50–5000 copies/ml)</th>
<th>HIV (&gt;5000 copies/ml)</th>
<th>HIV −</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC</td>
<td>0.31 (0.28–0.46), n = 25</td>
<td>0.26 (0.14–0.67), n = 15</td>
<td>0.13 (0.10–0.22), n = 24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.27 (0.17–0.47), n = 53</td>
</tr>
<tr>
<td>(CD123&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>0.11 (0.08–0.18), n = 26</td>
<td>0.09 (0.03–0.17), n = 15</td>
<td>0.09 (0.04–0.19), n = 24, NS</td>
<td>0.29 (0.13–0.42), n = 53</td>
</tr>
<tr>
<td>(BDCA-2&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>0.08 (0.02–0.18), n = 12</td>
<td>0.11 (0.07–0.17), n = 9</td>
<td>0.09 (0.06–0.13), n = 12, NS</td>
<td>0.37 (0.15–0.50), n = 21</td>
</tr>
<tr>
<td>Influenza-IFN-α</td>
<td>107 (49–325), n = 18</td>
<td>80 (26–180), n = 14</td>
<td>93 (36–189), n = 16, NS</td>
<td>1468 (626–2094), n = 34</td>
</tr>
<tr>
<td>HSV-1-IFN-α</td>
<td>164 (57–233), n = 18</td>
<td>54 (10–179), n = 14</td>
<td>84 (33–173), n = 16, NS</td>
<td>912 (672–1790), n = 35</td>
</tr>
<tr>
<td>CD4 counts</td>
<td>584 (279–694)</td>
<td>378 (312–607)</td>
<td>425 (271–600)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>b</sup> Results shown are measured in percentage of positive cells and picograms per milliliter for IFN-α, and values are expressed as median (25th–75th percentile). Statistical significance within the MDC subset is as follows: <50 copies/ml vs >5000 copies/ml, p < 0.0012, and 50–5000 copies/ml vs >5000 copies/ml, p = 0.029, respectively.
of 1246 and 651 cells/mm², had normal IFN-α responses. These data suggest that retention of the PDC subset may be possible in a small subset of patients highly responsive to antiretroviral therapy, as it was previously described for the long-term nonprogressor patients (20). Additional experiments isolating the PDC will be needed to determine whether a decrease in IFN-α secretion is due to a decrease in frequency of PDC or whether a functional impairment of this subset is also present.

Our data confirm a recent report by Feldman et al. (29) and support the association in HIV-infected patients between a decrease in IFN-α secretion and a decrease in the CD123⁺ DC subset, and extend it with the use of additional markers such as BDCA-2.

CD4 counts, viral load, and frequency of MDC

The overall frequency of MDC in patients remained stable with similar cell percentage as compared with uninfected controls (Fig. 2 and Table I). No correlation was found between MDC frequency and CD4⁺ T cell counts (data not shown). However, virally suppressed patients were found to have a significantly higher number of MDC (0.31% ; 7020 cells/ml) than patients with a viral load of >5000 copies/ml (0.13% ; 2636 cells/ml, p < 0.0032; Table III). An association between a decrease of MDC frequency with an increase of viral load was further indicated by a significant negative correlation between these variables (Rho = −0.5, p < 0.0001, n = 65). The inverse association between MDC and viral load was also sustained when the analysis was restricted to a subset of 21 patients not receiving treatment (Rho = −0.68, p = 0.0007). It is important to note that the extensive use of antiviral treatment in our cohort may have biased our study against the possibility to detect the previously reported decreases in MDC during HIV infection (18), specifically the prevalence of HIV-infected subjects with <5000 copies/ml that did not show a significant decrease in MDC frequency compared with healthy controls. Overall, these results are consistent with a decreased MDC frequency only at high viral loads that can be reversed following antiretroviral treatment in contrast to the early and persistent deficiency in the PDC subset measured in the same patients, as described above. A longitudinal analysis of the consequences of HAART-mediated suppression on each DC subset (i.e., recovery of number and function as a correlate of viral suppression) is needed to confirm our cross-sectional findings.

We show for the first time a differential depletion between the frequency and function of MDC and PDC subsets when analyzed in parallel under suppressive therapy. Our data complement previous observations describing the depletion of MDC and PDC in viremic or end-stage HIV-infected patients (20, 21, 28). However, our studies indicate a lack of full DC reconstitution upon HAART that may contribute to a sustained immune impairment in these subjects. While we document a phenotypic and functional preservation in the MDC subset in the virally suppressed patients and HAART-responding patients, alteration in the PDC subset appears to be an early event and associated with a sustained impairment of IFN-α production. The consequence of the lack of recovery of IFN-α production and PDC number on the innate and adaptive immune functions of the patients remains to be defined. For example, a decrease in viral-induced IFN-α secretion may also affect in part the immune reconstitution of NK cell function. Additional experiments should assess whether the loss of this subset from circulation reflects a cytopathic effect caused by the virus through direct infection of the PDC subset (30) or through viral-induced apoptosis, as described with measles virus infection (31, 32). A role for interactions between HIV-1 and PDC subsets is supported by the susceptibility of IL-3-cultured Lin−HLA-DR⁺CD11c⁺ cells to be infected in vitro by HIV-1 (30). It is also of interest to relate our findings to current treatment guidelines for HIV infection, as a delay in treatment of patients with viral loads above 5000 copies/ml, irrespective of CD4 T cell count, would not prevent a decrease of MDC and PDC that may bear on immune function in general.

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