Correspondence

The Contribution of Cytomegalovirus to Changes in NK Cell Receptor Expression in HIV-1–Infected Individuals

To the Editor—Gumá et al. [1] reported interesting findings regarding the influence of human cytomegalovirus (HCMV) infection on the proportion of CD56+ NK cells expressing inhibitory CD94/NKG2A and activating CD94/NKG2C C-type lectin-like receptors in HIV-1–infected individuals, compared with HIV-1–uninfected individuals. Although their results are in agreement with those of our previous article [2] showing that the proportion of CD56+ NK cells expressing NKG2C+ cells is higher overall in HIV-1–infected individuals than in HIV-1–uninfected individuals, they found no difference in the proportion of these cells between HIV-1–infected and HIV-1–uninfected individuals who were seropositive for anti-HCMV IgG [1]. They concluded that HCMV infection is the major determining factor influencing the distribution of these NK cell subsets in both HIV-1–infected and –uninfected individuals. Although we are in broad agreement with these conclusions, we would like to point out additional observations from our work that are relevant to the interaction between HCMV and HIV-1 infections and their influence on NK cell subsets.

The mean percentage for NKG2C+ cells and the range in the HIV-1–uninfected control cohort reported by Gumá et al. was much greater than that described in our article [1, 2]. This means that the fold increase in the proportion of NKG2C+ cells in HIV-1–infected individuals (either treatment naive or receiving highly active antiretroviral therapy [HAART] with plasma virus RNA loads <50 copies/mL of blood [below the limit of detection]), compared with that in HIV-1–uninfected individuals, was much greater in our study. There are 2 main possibilities for this discrepancy. First, our strategy for flow-cytometric analysis differed from that of Gumá et al., who gated on CD3+CD56+ cells. Second, the higher level of NKG2C+ cells in the HIV-1–uninfected cohort of Gumá et al., compared with our control group, could have resulted from known geographical variation in exposure to HCMV. For example, the seroprevalence of HCMV in adults in Madrid has been reported to be 78% and that in London to be 48% [3, 4]. To address these questions, we used the same flow-cytometric analysis as Gumá et al., to compare the proportions of NKG2C+ and NKG2A+ cells in 48 patients (92% male) receiving HAART and whose HIV-1 loads were below the limit of detection for >1 year; we compared these patients with 20 healthy control subjects (85% male) (table 1). Comparisons were also done after individuals were grouped according HCMV serostatus using an anti-CMV IgG ELISA (Biokit).

In agreement with the data of Gumá et al. and with our previous findings, we observed an overall increase in the proportion of NKG2C+ NK cells in HIV-1–infected individuals, compared with HIV-1–uninfected individuals (table 1). However, we observed a concomitant decrease in the proportion of NKG2A+ cells, as report-

Table 1. Proportions of NK cells expressing NKG2A or NKG2C, split by HIV-1 and human cytomegalovirus (HCMV) infection status.

<table>
<thead>
<tr>
<th>Infection status</th>
<th>Subjects, no.</th>
<th>Stained NKG2C cells</th>
<th>Stained NKG2A cells</th>
<th>Anti-HCMV IgG concentration, mean ± SD (range), IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD (range), %</td>
<td>P</td>
<td>Mean ± SD (range), %</td>
</tr>
<tr>
<td>HIV positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCMV negative</td>
<td>2</td>
<td>11.3 ± 1.7 (10.1–12.5)</td>
<td>.0499a</td>
<td>66.6 ± 3.8 (63.9–62.2)</td>
</tr>
<tr>
<td>HCMV positive</td>
<td>46</td>
<td>38.8 ± 23.7 (0.1–90.7)</td>
<td></td>
<td>37.3 ± 19.8 (4.4–84.5)</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>37.6 ± 23.9 (0.1–90.7)</td>
<td></td>
<td>38.5 ± 20.3 (4.4–84.5)</td>
</tr>
<tr>
<td>HIV negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCMV negative</td>
<td>11</td>
<td>7.7 ± 4.1 (2.6–16.0)</td>
<td>.1024b</td>
<td>56.7 ± 18.4 (32.3–91.3)</td>
</tr>
<tr>
<td>HCMV positive</td>
<td>9</td>
<td>15.8 ± 12.3 (2.5–37.8)</td>
<td>.0051b</td>
<td>56.4 ± 14.7 (39.2–76.7)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>11.3 ± 9.5 (2.5–37.8)</td>
<td>&lt;.0001c</td>
<td>56.6 ± 16.4 (32.3–91.3)</td>
</tr>
</tbody>
</table>

NOTE. NK cells were gated as CD3+CD56+ lymphocytes. Statistical comparisons were made using the Mann-Whitney U test.

a Percentage of NKG2A+ or NKG2C+ NK cells in HCMV-positive vs. HCMV-negative individuals.

b Percentage of NKG2A+ or NKG2C+ NK cells in HCMV-positive HIV-1–positive vs. HCMV-positive HIV-1–negative individuals.

c Percentage of NKG2A+ or NKG2C+ NK cells in HIV-1–positive vs. HIV-1–negative individuals.

d Anti-HCMV antibody titers in HCMV-positive HIV-1–positive vs. HCMV-positive HIV-1–negative individuals.
HCMV may be driving NKG2C+ NK cell infected individuals (table 1). This was confirmed in our experiments, which is indicative of HCMV-seropositive individuals, compared with HIV-1–uninfected HCMV-seropositive individuals (15.8% ± 12.3%; P = .0051) (table 1).

Importantly, we found that 46 of 48 HIV-1–infected individuals were positive for CMV IgG. In addition to the high seroprevalence, HIV-1–infected individuals have higher anti-HCMV antibody titers than HIV-1–uninfected HCMV-seropositive individuals, compared with HIV-1–uninfected HCMV-seropositive individuals (38.8% ± 23.7%), (table 1).

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References


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Reprints or correspondence, Dr. Martin R. Goodier, Dept. of Immunology, Imperial College London, Chelsea and Westminster Hospital, 369 Fulham Rd., London SW10 9NH, United Kingdom (m.goodier@imperial.ac.uk).

Reply to Mela and Goodier

To the Editor—In their letter, Mela and Goodier [1] report a study similar to ours [2] that used the same flow-cytometric analysis to compare the proportions of NKG2C+ and NKG2A+ cells in HIV-1–positive patients receiving highly active antiretroviral therapy and in healthy control subjects. They broadly agree with our conclusion that human cytomegalovirus (HCMV) infection appears to be the ma- jor factor determining an increase in the numbers of CD94/NKG2C+ NK cells in HIV-1–positive and –negative individuals.

A difference between the 2 studies was the greater proportions of NKG2C+ cells in our HIV-1–negative control subjects. As a consequence, the relative increase in the proportions of NKG2C+ in HIV-1–positive individuals, compared with those in HIV-1–negative subjects, was higher in the London study. The interpretation that this may reflect the known geographical vari- ation in exposure to HCMV is plausible; in addition, differences in age distribution between cohorts might be relevant. Irre- spective of this minor discrepancy, the re- sults of both studies support the idea that the higher susceptibility to HCMV infection, reinfection, and/or reactivation in HIV-1–positive individuals enhances its impact on the NK cell receptor repertoire.

In our article [3] that originally de- scribed changes in the NK cell receptor repertoire associated with HCMV sero- logical status, an important variability in the proportions of NKG2C+ cells among HCMV-seropositive blood donors was noticed. To explain this, we proposed [4]...