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Cross-Reactive T-Helper Responses in Patients Infected with Different Subtypes of Human Immunodeficiency Virus Type 1

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Immunization with a recombinant glycoprotein 160 envelope immunogen derived from a virus of genetic subtype B induced strong specific T-helper cell responses in asymptomatic human immunodeficiency virus (HIV) carriers infected with subtypes B to G. This indicates that the HIV-specific T-helper immunity, which is the basis for development of antibodies and cytotoxic T lymphocytes, can be improved by both homologous and heterologous antigens. It also suggests that a particular immunogen can be effective against many different HIV strains.

The extraordinary genetic diversity and rate of replication of human immunodeficiency virus type 1 (HIV-1) are major problems in the search for a prophylactic vaccine and in antiviral chemotherapy (5, 12). In many viral infections, immunity to the envelope and outer proteins is critical for viral clearance and control. The HIV infection is characterized by a continuous envelope and outer proteins is critical for viral clearance and chemotherapy (5, 12). In many viral infections, immunity to the envelope and outer proteins is critical for viral clearance and control. The HIV infection is characterized by a continuous envelope and outer proteins is critical for viral clearance and chemotherapy (5, 12). In many viral infections, immunity to the envelope and outer proteins is critical for viral clearance and control.
dium was used to correct for spontaneous proliferation. The mean radioactivity (counts per minute) was calculated for all triplicates of antigens, mitogens, and the medium control. To obtain a value for the specific proliferation, a stimulation index (SI) was calculated by dividing the mean counts per minute for each antigen or mitogen by the mean counts per minute for medium or control baculovirus. An SI above 3 was defined as a specific response.

Individuals infected with different subtypes of HIV-1 had a very low or no T-cell response to HIV antigens before immunization (Fig. 1). After immunization with rgp160 of subtype B, all HIV-infected individuals improved their capacity to respond immunologically to rgp160 of subtype B. This occurred in patients infected with subtypes C, D, E, F, and G in addition to B (Fig. 1). The responses were maintained at high levels during the whole period studied (Fig. 1b). Nonimmunized patients or individuals receiving placebo rarely responded. Reactivity to non-gp160 components of the immunogen was low (0 to 15% of the HIV-specific reactivity [not shown]). The increases in T-cell proliferative responses were HIV specific as determined by reactivity to rgp160 and/or gp120, but responses did not increase or they increased to a minor degree (<15%) to recall or control antigens (9).

We also evaluated the T-cell reactivity to native gp120 derived from virions of isolates from subtypes A to E as well as a recombinant preparation of gp120. Nine patients who themselves were infected with HIV-1 of subtype B developed significant reactivities to the native gp120 antigens (Table 1). Reactivity to the B envelope antigen developed in all nine individuals after immunization with gp160 of subtype B. One patient infected with subtype C and immunized with subtype B

![Graph](image)

**FIG. 1.** (a) Magnitudes of specific T-cell responses to rgp160 before and after immunization at all time points (788 assays in total) for 36 patients infected with HIV-1 subtypes B to G (the median and 25th and 75th percentiles, as well as 10th and 90th percentiles, are shown). Single values are shown preimmunization for subtype C and postvaccination for subtype D. (b) Specific T-cell responses over time to rgp160 of subtype B in patients infected with subtype B, C, D, E, F, or G. The patients were immunized either with rgp160 of subtype B or placebo (alum). All time points were not evaluated for all patients, but there is at least one pre- and one postvaccination assay for each subtype. Mean responses from both nonimmunized (n = 400) and noninfected individuals (n = 400) represent control values.

**TABLE 1.** HIV-specific T-cell responses to native preparations of gp120 derived from different genetic subtypes

<table>
<thead>
<tr>
<th>Activating antigen</th>
<th>№. of responders/no. tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>rgp160-immunized infected patient(s)</td>
<td>Placebo recipient(s)</td>
</tr>
<tr>
<td>Subtype B</td>
<td>Subtype C</td>
</tr>
<tr>
<td>Native gp120</td>
<td></td>
</tr>
<tr>
<td>Subtype A</td>
<td>3/9</td>
</tr>
<tr>
<td>Subtype B</td>
<td>7/9</td>
</tr>
<tr>
<td>Subtype C</td>
<td>5/9</td>
</tr>
<tr>
<td>Subtype D</td>
<td>3/9</td>
</tr>
<tr>
<td>Subtype E</td>
<td>2/9</td>
</tr>
<tr>
<td>rgp160 of subtype B</td>
<td>8/9</td>
</tr>
<tr>
<td>rgp160 of subtype B</td>
<td>25/25</td>
</tr>
</tbody>
</table>
reacted to the native gp120 of subtypes B, D, and E. Placebo recipients did not react with any of the envelope antigens (Table 1). Thus, 7 out of 10 tested immunized individuals responded to native gp120 from at least one other subtype in addition to subtype B, whereas a placebo recipient did not respond to any gp120 antigen (Table 1). The nine vaccinated individuals in Table 1 were evaluated at only one time point for these specific native antigens. A responder was defined as an individual responding with a SI above 3, as described above. Due to the fact that the study was blinded at the time the assay was performed, there were nine vaccinated individuals and only one placebo recipient. Specific responses to HIV antigens are very low or nonexistent before immunizations, as shown by placebo and preimmunization values. For the placebo recipient in this particular case the subtype is not known, but for the placebo patients that were investigated for rgp160 or rgp120, the subtypes were B to G.

These data indicate that it is possible to induce cross-subtype HIV-specific T-cell proliferative responses in patients already infected with another HIV-1 subtype. Immunized individuals infected with any one of the subtypes B, C, D, E, F, and G responded to antigen of subtype B. Most patients also responded to at least one more subtype antigen in addition to B. Such responses were low or nonexistent before immunization.

For protection against a primary HIV infection, we envisage that both a primary local humoral and a cell-mediated immunity in mucosa are needed. Following the primary infection, a strong specific T-helper response and a systemic cytotoxic T-cell response appear to be associated with a better prognosis (18, 19). It is desirable to induce this second barrier, which should include cellular responses at all levels, such as T-helper cells, natural killer cells, antibody-dependent cellular cytotoxicity, and CTLs. However, it is only the CTL response that persists naturally for any demonstrable period.

HAART can potently and durably reduce HIV-1 replication in vivo, but there are now indications that even prolonged treatment will not result in total eradication of replication-competent virus in PBMCs. In order to be able to eradicate the virus, probably new therapeutic approaches must be considered in combination with HAART. These approaches may need to include both an activation of resting CD4 T cells and stimulation of the HIV-1-specific immunity (11). Therapeutic vaccination with rgp160 yields strong HIV-specific T-helper-cell responses and has a modest positive effect on CD4 counts but does not have any effect on viral load (9, 20). HAART alone does not seem to affect the HIV-specific T-helper-cell responses but reduces viral load. This suggests that a combination of HAART and immunization would improve the total effect. The finding that cross activation of the T-helper response can also occur in patients infected with subtypes other than that of the immunogen, gives hope that HAART can be combined with immunogens that do not have to represent all locally thriving strains or subtypes of HIV.

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