IL-6 and CRP Levels Are Associated with mMDSC Frequencies in HIV+ Individuals on ART

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ABSTRACT# 2159

BACKGROUND

Myeloid-derived suppressor cells (MDSCs) are heterogeneous immature or progenitor myeloid cells that undergo expansion in pathologic conditions under the influence of GM-CSF and various inflammatory cytokines.

Human MDSCs are characterized by several differing phenotypes, two of which we evaluated in this study:

- Monocytic (mMDSCs): CD11b+CD14+CD33+HLA-DR+
- Classical (cMDSCs): Lin-CD33+HLA-DR-

There is increasing evidence that MDSCs play an integral role in the inflammatory milieu of HIV infection and frequency of MDSCs in ART-naive individuals has been shown to correlate significantly with expression of regulatory T-cells.

Additionally studies suggest that MDSC expression is associated with viral load and inversely related to immune reconstitution in early HIV infection.

There are still significant knowledge gaps regarding the role of MDSC subsets in chronic, virally suppressed HIV infection.

STUDY OBJECTIVES

- To describe the frequency of immunoregulatory cell populations in treated chronic HIV infection compared to seronegative controls in the Pittsburgh MACS.
- To explore any relationships between immunoregulatory populations and levels of immune activation and inflammation.
- To describe associations between immunoregulatory cell populations and monocytic subsets in HIV+ and seronegative controls.

DEMOGRAPHICS AND METHODS

Characteristics HIV+ Control

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV+</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Median Age</td>
<td>43.0</td>
<td>42.5</td>
</tr>
<tr>
<td>Race</td>
<td>CA</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>AF</td>
<td>3</td>
</tr>
<tr>
<td>Median Years Infected</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Median Years Suppressed</td>
<td>6</td>
<td></td>
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<tr>
<td>Median CD4+ T cell count (counts/mm3)</td>
<td>803</td>
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Flow cytometry:
- Cryopreserved PBMC at week intervals
- Single, Live/Dead, CD3, CD4, CD8, CD14, CD16, CD56, CD11b, CD23, HLA-DR, CD80

Analytical methods:
- Plasma IL-6, hsCRP, and sCD163 were measured at three visit time points at 4 week intervals.

RESULTS

- Plasma levels of IL-6, hsCRP, and sCD163 were similar across time periods and between groups.
- Plasma levels of IP-10 and sCD14 remained elevated in the HIV+ group compared to seronegative controls (SN).
- There was no difference in MDSC frequencies between the time points.
- There was a positive correlation between plasma IL-6 and hsCRP levels with mMDSC frequencies in the HIV+(+) this was absent in SN controls.
- Plasma IL-6 and hsCRP levels in HIV+(+) participants were not significantly different from the seronegative controls (not shown).

CONCLUSIONS AND IMPLICATIONS

- Although levels of IL-6, hsCRP, and sCD163 are similar between HIV(+) participants and seronegative controls, plasma levels of sCD14 and IP-10 are higher in the HIV(+) group despite prolonged viral suppression on ART and CD4+ T cell reconstitution.
- Frequencies of monocyte subsets as well as classic and monocytic MDSCs are similar between the two groups.
- However, in HIV(+) individuals, mMDSC frequency directly correlated with IL-6 and hsCRP concentration, corroborating evidence that MDSC expansion is dependent on IL-6 levels.
- Among seronegative controls, there is inverse correlation between IP-10 and IL-6 and frequencies of mMDSCs. This relationship disappears in HIV(+) participants. Given that IP-10 and sCD14 remain elevated in HIV(+) participants despite treatment, the loss of correlation suggests an inability of MDSCs to control inflammation and monocyte activation in chronic HIV infection.
- Our results suggest that the persistent inflammation and immune activation associated with chronic, treated HIV infection is partly due to the inability of immunoregulatory mechanisms in HIV infected individuals to control ongoing inflammation.
- Further research is necessary to delineate the exact role of different MDSC subsets in chronic HIV immunopathogenesis.

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