The association between plasma microbiome and anti-CD4 autoantibodies in HIV pathogenesis

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Background

Although long-term antiretroviral therapy (ART) significantly suppresses viral replication and controls HIV disease, HIV-infected patients with poor CD4+ T cell recovery have exacerbated disease progression, and increased morbidity and mortality, compared to HIV-infected patients with CD4+ T cell counts above 500 cells/μL (Lederman, 2011; Hunts, 2009).

**Immunologic responders:** Aviremic ART-treated patients with peripheral CD4+ T cell counts > 500 cells/μL

**Immunologic non-responders:** Aviremic ART-treated patients with peripheral CD4+ T cell counts < 350 cells/μL

**Potential mechanisms of poor CD4+ T cell reconstitution**

- Persistent immune activation
- Lymphoid fibrosis and thymic insufficiency

However, a mechanism specific to direct CD4+ T-cell destruction in viral suppressed patients is not known.
CD4+ T cell depletion but not CD8+ T cell depletion characterizes HIV immunologic non-responders

$T$ cell counts (cells/μl)

**CD4 count**

- Healthy
- CD4high
- CD4low

$P < 0.0001$

**CD8 count**

- Healthy
- CD4high
- CD4low

$P = 0.32$
Increased plasma anti-CD4 IgG levels in aviremic ART-treated immunologic non-responders, and its association with peripheral CD4+ T cell counts

Patients

- $r = -0.53$, $P = 0.0002$

Graphs showing distributions of anti-CD4 IgG levels and CD4+ T cell counts across different groups: Healthy, CD4high, CD4low, and long-term non-progressor. Significance levels indicated by $P < 0.0001$, $P < 0.001$, and $P < 0.05$.
Antibody-dependent cytotoxicity

Anti-CD4 IgG: 0 μg/ml 0.625 μg/ml 1.25 μg/ml 2.5 μg/ml 5 μg/ml

SSC-A

CD3

24.5% 18.8% 15.2% 11.3% 7.91%

P < 0.0001

P < 0.0001

%cytolysis of CD4+ T cells

NK CD4

NK CD4

lymph node

Anti-CD4 IgG

FcR

CD4

CD4

Control -1

Control -2

Positive control

P < 0.0001
Plasma microbiome

- anti−CD4 IgG baseline < 50
- anti−CD4 IgG baseline > 50

- bedis1
  - method = "bray"
  - PCoA 1
  - PCoA 2

- Plasma microbiome
  - aCD4 IgG\textsuperscript{low}
  - aCD4 IgG\textsuperscript{high}

- Class level Taxonomy

- Percentage

- aCD4 IgG\textsuperscript{high}
- aCD4 IgG\textsuperscript{low}
Plasma microbiome in patients

**Diversity**

<table>
<thead>
<tr>
<th>Gini-Simpson Index</th>
<th>aCD4 IgG$^{\text{high}}$</th>
<th>aCD4 IgG$^{\text{low}}$</th>
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<tbody>
<tr>
<td>0.950</td>
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**Genus-level of bacteria**

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<th>Genus</th>
<th>Relative abundance (%)</th>
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<td>faucicola</td>
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<td>methylophilus</td>
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<tr>
<td>stenotrophomonas</td>
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<td>methylophilus</td>
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</table>
Conclusions

• HIV+ immunologic non-responders had reduced CD4+ T cell counts, elevated B cell activation and increased plasma anti-CD4 autoantibodies compared to HIV+ responders under viral suppressive ART.

• Plasma anti-CD4 IgG levels correlated with poor CD4+ T cell recovery only among HIV-infected individuals.

• Anti-CD4 IgG purified from plasma of HIV+ non-responders induced CD4+ T cell death through ADCC in vitro.

• Plasma certain bacterial products were associated with anti-CD4 IgG in patients.

• These results suggest a causal and pathologic role of anti-CD4 Abs in blunting CD4+ T cell recovery in HIV-infected individuals despite viral suppression on ART.
• Due to these data, we propose a model in which HIV infection induces a “leaky” gut.

• This leaky gut results in elevated systemic microbial translocation and chronic B cell activation, and pathologic antibody production.

• These anti-CD4 Abs then mediate CD4+ T cell death through Ab-dependent cytotoxicity (ADCC) which blunts CD4+ T cell recovery and contributes to increased morbidity and mortality in HIV+ non-responders.

• In this context, the present work reveals a novel CD4-specific mechanism capable of leading to incomplete immune reconstitution in HIV+ non-responders.
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Anti-CD4 monoclonal antibody generation and bacterial product biologic analysis

Collaborators needed:
- Protein purification, antigenic mutation and modification design, and structure analysis
- Bacterial product biological and functional analysis