Increased frequency of circulating follicular helper T-cells (T_{FH}) in patients with Granulomatosis with Polyangiitis


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Introduction:
Involvement of T-cells in the pathogenesis of GPA
- T-cells infiltrate in granulomatous lesions
- Upregulation of T-cell activation markers
- Therapeutic effect of anti-thymocyte globulin (ATG)

Disclosure
I have no conflict of interest in relation to this presentation.

Introduction:
Ongoing T-cell activation & defect in T_{Reg} function in GPA

Effector CD4 T-cell subsets
- Protects from intracellular bacterial infections
- IL-12

Protection from intracellular bacterial infections

Promotes neutrophil recruitment to infected tissue

IL-6 / TGFβ

IL-4

IL-17

B-cell class switching

Antibody production

IL-21
**Introduction:**

**IL-21: implications for autoimmune diseases**

- Blockade of IL-21 activity reduces joint inflammation and destruction in arthritis animal models. (Young DA et al. Arthritis Rheum 2007)
- Blockade of IL-21 activity reduces levels of anti-dsDNA and prevents renal disease in mouse models of SLE. (Balan AH et al. PNAS 2008)
- IL-21R deficient mice are protected against the development of IBD and type-1 diabetes. (Fina D et al. Gastroenterology 2008, Spolski R et al. PNAS 2008)
- Genome-wide association studies in human: Polymorphisms within the IL-21 gene are associated with SLE, IBD, and psoriasis.

**Aim of the study**

**To explore a possible role of T_{FH} cells in the immunopathogenesis of Granulomatosis with Polyangiitis**

**Study population**

**Clinical and laboratory characteristics of the GPA patients**

<table>
<thead>
<tr>
<th></th>
<th>GPA in remission</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>No. male / no. female</td>
<td>21 / 19</td>
<td>15 / 12</td>
</tr>
<tr>
<td>Age, median (range) years</td>
<td>59 (28 - 81)</td>
<td>56 (26 - 72)</td>
</tr>
<tr>
<td>No. positive / negative for ANCA</td>
<td>23 / 17</td>
<td>**</td>
</tr>
<tr>
<td>No. receiving / not receiving treatment</td>
<td>11 / 29</td>
<td>**</td>
</tr>
<tr>
<td>No. with localized / generalized</td>
<td>12 / 28</td>
<td>**</td>
</tr>
</tbody>
</table>

*Treatment with azathioprine only*

**In vitro stimulation and flow cytometric analysis**

**Increased circulating T_{FH} cells in ANCA_{pos} GPA**

**Increased Bcl-6 mRNA levels in ANCA_{pos} GPA**
IL-21 induces IgG production in B-cells of GPA

The pathogenic role of T<sub>FH</sub> cells in GPA

Conclusions

Increased frequencies of circulating T<sub>FH</sub> cells producing IL-21 in ANCA<sub>pos</sub> patients suggest a role for these cells in the immunopathogenesis of GPA. Blockade of IL-21 could constitute a new therapeutic strategy for GPA.

Circulating naïve and memory CD4 T-cell subpopulations in GPA-patients in remission and active disease

Decreased %Naive CD4 T-cells and increased %Effector memory CD4 T-cells in GPA-patients in remission

Acknowledgments

Dept. of Rheumatology & Clinical Immunology
- Prof. Dr. C.G.M. Kallenberg
- Dr. H. Tadema
- Dr. A. Rutgers
- Ms. M. Huitema
- Ms. B. Doornbos-van der Meer

Dept. of Pathology & Medical Biology
- Prof. Dr. P. Heeringa
- Drs. N. Lepse

Dept. of Nephrology
- Prof. Dr. C.A. Stegeman

Dept. of Laboratory Medicine
- Prof. Dr. P.C. Limburg

Abdulahad et al. Kidney Int. 2006
Introduction:

**Actions of IL-21:**

- B cells
- ANCA ??
- Granuloma formation ??
- Cytotoxicity
- Perforine
- Granzymes
- Tissue injury ?

The pathogenic role of **T\textsubscript{FH}** cells in GPA

ACR 2011