**Complement system in rheumatic diseases**

**The complement system**

- Classical pathway
  - Activation of C3
  - Deposition of C3b
  - C3-convertase
  - Release of anaphylatoxins
  - Membrane Attack Complex (C5-9)

- Alternative pathway
  - Activation of C3

- Lectin pathway
  - MBL, ficolins
  - C1r, C1s, C1q

**Spontaneous hydrolysis**

C3 → C3b → C3a

**Diseases associated with excessive complement activation**

- Ischemia/reperfusion (stroke, bypass)
- Transplantation (xeno)
- Burn injuries
- Dialysis
- Asthma
- SLE
- Rheumatoid arthritis
- Haemolytic uremic syndrome
- Sepsis
- SLE
- Rheumatoid arthritis
- Haemolytic uremic syndrome
- Sepsis
- SLE
- Rheumatoid arthritis
- Haemolytic uremic syndrome
- Sepsis
- SLE
- Rheumatoid arthritis
- Haemolytic uremic syndrome
- Sepsis

**CRP in Lund epidemiologic cohort of patients with rheumatoid arthritis**

- N > 1000 at each time point
- Methotrexate
- TNF-inhibitors

**0.7% adults in Sweden**

- More often women
Evidence that complement is involved in RA

- Complement consumption from blood in flares
- Complement fragments in synovial fluid and on synovial membrane
- Genetic analysis in animal models
- Knock-out mice are resistant

**Active complement**

**Complement inhibited**


Human cartilage

Fibromodulin activates complement

**COMP** is produced in chondrocytes
Used as marker for joint destruction

Cartilage oligomeric matrix protein (COMP) activates alternative pathway

Assay measuring COMP-C3b complexes
Arthritis development in mice vaccinated against C5a

SLE: systemic lupus erythematosus

Autoantibodies, immune complexes = complement activation = inflammation

7000 in Sweden
90% women
flares
autoantibodies

Neutrophil extracellular traps (NETs)

- Secreted chromatin
- Mainly from neutrophils
- Concentrate anti-bacterial enzymes
- To catch/kill bacteria
- Induced by LPS + IL 8, PMA, C5a, bacteria, fungi, platelets

NETs in SLE?

- Autoantibodies in SLE patients against: DNA, histones, nuclear antigens
- NETs that are not removed may be acting as source for these antigens
- NETs are degraded by DNAsae in serum and SLE patients have low DNAsae activity
- NETs can potentially activate complement?
**SLE Disease Activity Index (SLEDAI)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>High degrading (n = 67)</th>
<th>Low degrading (n = 27)</th>
<th>p-value (Pearson)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>1 (1.5)</td>
<td>0 (0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>5 (7.5)</td>
<td>2 (7.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Lupus headache</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (1.5)</td>
<td>1 (3.5)</td>
<td>2.000</td>
</tr>
<tr>
<td>Meningitis</td>
<td>8 (12)</td>
<td>3 (11)</td>
<td>0.9</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>10 (15)</td>
<td>3 (11)</td>
<td>0.99</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (6)</td>
<td>4 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (9)</td>
<td>7 (26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Leukopenia b</td>
<td>6 (9)</td>
<td>4 (15)</td>
<td>0.4</td>
</tr>
<tr>
<td>Low complement</td>
<td>30 (45)</td>
<td>22 (81)</td>
<td>0.001</td>
</tr>
<tr>
<td>dsDNA antibodies</td>
<td>20 (30)</td>
<td>25 (93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>2 (3)</td>
<td>3 (11)</td>
<td>0.9</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>4 (6)</td>
<td>3 (11)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**NETs activate complement**

**Opsonisation with complement increases antibody production against antigens**

**Follow up of SLE patients**

**Antibodies affect NET degradation**
NETs are not degraded \rightarrow \text{NETs activate complement} \rightarrow \text{More antibodies against NETs produced}

\text{Complement inhibitors}

\text{Mutated in hemolytic uremic syndrome}
\text{and age related macula degeneration}

\text{SLE patients carrying mutations in complement inhibitors CD46/FH develop nephritis earlier}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{sle_patients}
\caption{SLE patients carrying mutations in complement inhibitors CD46/FH develop nephritis earlier}
\end{figure}

Conclusions

✓ some cartilage molecules activate complement, which may contribute to joint damage in arthritis
✓ mutations in complement inhibitors accelerate onset of nephritis in SLE
✓ impaired degradation of NETs may lead to activation of complement and autoantibody production in SLE
✓ involvement of complement in pathology of SLE and rheumatoid arthritis opens for novel diagnostic tools and treatments