The Complement System: Friend and Foe

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Disclosures

- I have received honoraria and research funding from Alexion
Overview

- Complement function and regulation
- Implications of chronic uncontrolled complement activation
- PNH, aHUS diagnosis and management
Design of complement

- Now known to be at least 27 proteins

Initiation
- Infection
- Surgery
- Autoimmune disease
- Pregnancy

Function: LYSIS
Localization on membrane surfaces
Activation and amplification (3 pathways)
Regulation
Inactive state (serum)

The Complement Cascade

- **Lectin Pathway**
  - Immune Complex Clearance
  - Microbial Opsonization

- **Classical Pathway**
  - C3 + H₂O - ALWAYS ACTIVE (chronic)
  - Amplification

- **Alternative Pathway**

**Proximal**

**C3**

**Terminal**

- **C5a**
  - Potent Anaphylatoxin
  - Chemotaxis
  - Proinflammatory
  - Leukocyte Activation
  - Endothelial Activation
  - Prothrombotic

- **C5b-9**
  - Membrane Attack Complex
  - Cell Lysis
  - Proinflammatory
  - Platelet Activation
  - Leukocyte Activation
  - Endothelial Activation
  - Prothrombotic
Regulation of Complement
Regulation gives specificity

Activated complement

Complement attacks both self and non-self

Host cells are protected by complement regulatory proteins
Control of complement

- Direct inhibition of enzyme activity
- Disruption of enzyme complexes
- Degradation of C3b and C4b
- Prevention of MAC assembly

C1 inhibitor
CD59
CD55
Factor I and cofactors (Factor H, C4 binding protein, MCP, TM)

MCP = membrane cofactor protein; TM = thrombomodulin; TCC = terminal complement complex.
Factor I and co-factors: Soluble and Membrane Bound Complement Regulators
CD55 and CD59: Membrane Bound Complement Regulators
Chronic Uncontrolled Complement Activation Leads to Devastating Consequences

Proximal:
- Opsonization
  - aHUS: Chronic uncontrolled complement activation (loss of Factor H, I, MCP or TM)
  - PNH: Loss of CD59, CD55

C3 + H₂O - ALWAYS ACTIVE (chronic)

Amplification

Alternative Pathway
- Natural Inhibitors: Factor H, I, MCP, CD55

Classical Pathway
- Natural Inhibitor: CD55

Lectin Pathway

Terminal:
- C5a
  - Inflammation
  - Consequences: Anaphylaxis, Inflammation, Thrombosis
- C5b-9
  - Membrane Attack Complex
  - Cell Lysis
  - Consequences: Cell Destruction, Inflammation, Thrombosis

Consequences
Consequences of deregulation
# Diseases of disordered complement regulation

<table>
<thead>
<tr>
<th></th>
<th><strong>PNH</strong></th>
<th><strong>aHUS</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Aetiology</strong></td>
<td>Acquired PIGA mutation, resulting in deficiency of CD55 and CD59</td>
<td>Inherited mutation or acquired inhibitor of Factor I or co-factors</td>
</tr>
<tr>
<td><strong>Tissue affected</strong></td>
<td>Haematopoietic</td>
<td>Endothelial</td>
</tr>
<tr>
<td><strong>Age at presentation</strong></td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Pathogenetic event</strong></td>
<td><strong>Chronic</strong> attack on vulnerable tissue by activated complement</td>
<td></td>
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<tr>
<td><strong>Clinical effects</strong></td>
<td>Intravascular haemolysis, thrombosis, renal failure, pulmonary HT, fatigue, smooth muscle spasm, pain</td>
<td>Thrombotic microangiopathy, renal failure, neurological abnormalities</td>
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</tbody>
</table>
Loss of Factor I and co-factors: Chronic Uncontrolled Complement Activation

- Simple triggers, including common infections and stressors further accelerate complement over-activity

Atypical HUS

- Very rare (about the same as PNH)
- Inherited deficiency or acquired inhibitor of I, H, TM, etc
- May present from infancy to old age
- Presents like TTP: microangiopathic haemolytic anaemia with thrombocytopenia, RBC fragmentation, renal failure
  - But ADAMTS13 >10%
- Transient response to PLEX
- Progresses to ESRD; recurs in transplant kidneys
No CD55/CD59
Unrestrained activation of terminal complement...
In PNH Chronic Uncontrolled Complement Activation Leads to Vasoconstriction and Thrombosis

Summary: Disorders of Complement Regulation

Erythrocytes → CD55/59 → Intravascular haemolysis
CD55/59 → Factor I → Endothelium

Complement is always on

TMA
Diagnosis

PNH
- Bone marrow failure
- Weird thrombosis
- Intravascular haemolysis
- Haemoglobinuria

aHUS
- MAHA (like TTP)
- ADAMTS13 >10%
- Not responding to PLEX

HIGH-SENSITIVITY FLOW

GENETIC TESTING*
Treatment of complement regulation disorders
Eculizumab blocks terminal complement

Binds with high affinity to C5\textsuperscript{1,2}

Terminal complement: C5a and C5b-9 formation blocked\textsuperscript{1,2}

Proximal functions of complement remain intact\textsuperscript{1,2}:
- Weak anaphylatoxin\textsuperscript{2,4}
- Immune complex clearance\textsuperscript{2}
- Microbial opsonization\textsuperscript{2}
Eculizumab blocks haemolysis in PNH

- 87.6% serum LDH reduction 1 month after treatment initiation\(^1\)
- 86.9% decrease in hemolysis maintained for 36 months\(^1\)

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Impact on survival in PNH

**Pre-eculizumab from time of diagnosis in 80 patients with PNH**

- Despite best supportive care, 5-year mortality rate was 35%.

**PNH patients on eculizumab compared with age- and gender-matched controls**

- Hazard ratio = 2.24 (p = 0.013)

*Survival after 10 years is slightly inferior to controls with causes of death related to bone marrow failure and not hemolysis or thrombosis.


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aHUS: Improvement in GFR with eculizumab treatment

Petra Muus et al. Blood 2013;122:2186
Wrap-up
Complement: friend and Foe

- Complement is an important part of the innate immune system
  - Always ‘on’, ramped up when needed
- Multiple complement defense proteins protect host tissues
- Acquired or congenital deficiencies in complement defense proteins
  - CD55/59 → PNH
  - Factor I and friends → aHUS
- Complement inhibition with eculizumab is effective treatment