Lecture 17: Attack by Complement and Counterattack by Microbes

Review Concepts of Complement

Complement was addressed in Lecture 3

Major first line of defense (innate immunity)

Major functions:
- Opsonization
- Cell Lysis
- Activation of phagocytic cells

Overview of Complement
Complement as an Important Bridge

Complement Evasion - General

Recognition of Conserved Cell wall Features
Evasion of Toll-like Receptors (TLR)

Pathogens can modify targets of innate immunity.

The gram-negative bacteria Salmonella and Yersinia can change their LPS structure, making it less stimulatory for TLR4.

Many pathogens down-regulate their flagellin genes upon entry into the host. This prevents recognition by TLR5.

Streptococcus pneumoniae produces >100 types of capsular polysaccharide

Complement: Added Features - Lambris, 2008
Complement Pathways

- Complement Activation
  - Proteins are normally inactive - need to be activated (or transient)
  - Activation - sequential proteolysis
  - Covalent Attachment - become stably active after attaching to invruding (ab complexes)
  - Regulation - important to minimize complement mediated damage to host cells

Complement Regulation

- Regulators of Complement Activation (RCA)
  - Proteins that regulate complement
  - Structurally similar proteins
  - Complement receptor 1 (CR1)
  - Factor H (fH)
  - C4-binding protein (C4BP)
  - Decay accelerating factor (DAF)

Complement Regulation - Complexity

- Regulation
  - C3a, C5a, C3b, C5b-9
  - CI, C1r, C1s
  - C4, C2, C3, C5, C6, C7, C8, C9

- Normal conditions
  - opsonizing activity for phagocytosis
  - TCC - CD59

- Inhibition of C3 convertase
  - C3bBb - CI activation
  - C3b - C3 convertase
  - C4b2a - C3 convertase
Complement Activation Regulators

<table>
<thead>
<tr>
<th>Complement Activation Regulator</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>C1 inhibitor (C1 INH)</td>
<td>C1a, C1r, C2, C4, C5</td>
</tr>
<tr>
<td>Factor I</td>
<td>C1r, C1s, C2, C4, C5</td>
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<tr>
<td>Factor H</td>
<td>C2, C4, C5</td>
</tr>
<tr>
<td>Complement protein C1</td>
<td>C2, C4, C5</td>
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<tr>
<td>Complement protein C2</td>
<td>C2, C4, C5</td>
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<tr>
<td>Complement protein C3</td>
<td>C2, C4, C5</td>
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<tr>
<td>Complement protein C4</td>
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<tr>
<td>Complement protein C5</td>
<td>C2, C4, C5</td>
</tr>
</tbody>
</table>

C1 Inhibitor Regulation

C1q binds to antigen-complexed antibodies, resulting in activation of C1r2s2.

C1 INH prevents C1r2s2 from becoming proteolytically active.

Inhibition of C3 Convertase Formation

Formation of C4b2a complex (classical pathway C3 convertase) - DAF, MCP, and CR1 displace C2b from C4b.

Formation of C3bBb complex (alternative pathway C3 convertase) - DAF and CR1 displace Bb from C3b.
Factor I mediated cleavage of C3b

Complement: Added Features - Lambris, 2008

Mechanisms of Complement Evasion

Three main strategies addressed in review

Making use of the host's arsenal - acquiring regulators
- adaptations by binding RCA that circulate
- RCA are the natural regulators
- Recruitment and mimicry

Cutting through complement - pathogen proteases

Direct interventions - microbial complement inhibitors
Complement Evasion (Lambris, 2008)

Factor H as a Complement Regulator

What is Factor H?

- 150 kDa glycoprotein
- Circulates in plasma (0.5 - 0.8 mM concentration)
- Central role in regulating Alternative Pathway

How does Factor H regulate complement?

- Binds to complement factor-3b, making inactivated complement factor-3b (iC3b) susceptible to cleavage by complement factor I, and by interfering with the binding of properdin factor B (complement factor B) to complement factor C3b

Factor H in Complement Regulation

A Activation

- Amplification of complement activation

B Inactivation

- CCP 16-20
- Factor H
Role of Factor H

Pathogen proteins that bind complement

Evading Complement Regulation
Mechanisms of Complement Evasion

Three main strategies addressed in review

Making use of the host's arsenal

Cutting through complement
  pathogen proteases (almost exclusively bacteria)

Direct interventions - microbial complement inhibitors

Complement Evasion (Lambris, 2008)

Complement Evasion - Proteases

Examples:
  all these proteases cleave C1q

  Pseudomonas spp.
  Alkaline protease (PaAP)
  elastase (PaE)
  Porphyromonas spp. - PrtH

These proteases are also capable of cleaving Ig molecules!

End result: prevents activation of classical pathway
Complement Evasion - Proteases

Examples:
- All these proteases cleave C3
  - Pseudomonas spp.
  - Alkaline protease (PaAP)
  - Elastase (PaE)
  - Porphyromonas spp. - PrtH
End result: inactivation of C3 by cleavage into non-functional subunits different from C3α and C3b.

Complement Evasion - Proteases

Examples:
- All these proteases cleave C5a
  - Serratia marcescens
  - 56 kDa protease (no formal name)
  - Streptococcus spp.
  - scpA
  - scpB
End result: disassembles the pro-inflammatory signaling cascade.

Mechanisms of Complement Evasion

Three main strategies addressed in review
- Making use of the host's arsenal
- Cutting through complement
- Direct interventions
  - Microbial complement inhibitors
  - Destabilize complement efficiency
  - Only a few direct inhibitor have been identified
  - Most characterized from Staphylococcus aureus
Complement Evasion - Direct Inhibition

Examples:
- *Borrelia burgdorferi*
  - CD-59 like protein (binds C9, C8)
- *Streptococcal spp.*
  - SIC (streptococcal inhibitor of complement)
- *Schistosoma spp.*
  - Paramyosin (binds C9, C8)

End result: able to inhibit MAC formation

Complement Evasion - Direct Inhibition

Examples:
- Complement C2 receptor trispanning (CRIT)
- *Trypanosoma spp.*
  - CRIT
- *Schistosoma spp.*
  - CRIT

End result: disrupts interaction between C2 and C4 prevent CP convertase formation