“A brief introduction to the complement system”

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Bordet (1895): Complement lysis

1. Bacteria + Antiserum $\rightarrow$ Lysis

2. Bacteria + Antiserum $^{(56^\circ \text{C}, 30\text{'})}$ $\rightarrow$ No lysis

3. Experiment 2 + Normal serum $\rightarrow$ Lysis

4. Bacteria + Normal serum $\rightarrow$ No lysis

Conclusion:
Heat stable (Ab) and heat labile (C) factor
Complement in 1984

Meeting in Royal Society, London.
Hobart M. Immunology Today, 1985;5:212.

“Many immunologists hold that complement is baffling or irrelevant or, most conveniently, both but a recent meeting emphasized that complement is interesting and that it may be important, even only as an elegant model system.”
Cascade Principles
"Undetonated bombs"

P=Proenzyme
E=Enzyme

External activator
Auto-activation

Inhibition

Biological effects
Local vs. systemic

"The point of no return"
Cross-talk between cascades

Complement

Coagulation Fibrinolysis

Kallikrein-Kinin

C1-INHIBITOR
Functions of Complement

- **Protects the host against danger**
  - Fights infections
  - Cross-talks with other protective systems (e.g. TLR, B- and T-cells)
- **Contributes to tissue homeostasis**
  - Physiologic renovation (e.g. C1q/SLE)
  - Tissue repair and regeneration
- **Consequences of activation/dysregulation**
  - *Inflammation*
  - Tissue damage and disease
What is inflammation?

Heat  Redness  Swelling  Pain  Reduced function
Danger to the host

Danger -> 3 Rs

Host

Recognition
Response
Resolution
Danger signaling

Pattern recognition receptors/molecules (PRR/PRM):
- Host receptors of Innate Immunity (complement/TLR)

Ligands for PRRs:
- **PAMP**: Pathogen Associated Molecular Patterns
  - “external” (exogenous) danger - microbes
- **DAMP**: Damage Associated Molecular Patterns
  - “internal” (endogenous) danger - host molecules

Disturbed molecular homeostasis
Recognition by Complement

Pathway → Classical
Patterns for recognition
Ag-Ab complexes, CRP, SIGN-1, Phosphatidylserine

Lectin
Microbial molecules
Mannose, (IgA, IgM)

Alternative
Microbial molecules
Lipooligosaccharides

Recognition molecules
C1q
C1r, C1s

C4
C2

C3
C5 convertases

Inflammation
Direct C5 activation

Terminal pathway
sC5b-9
C5b-9(m)

C3bBbP

Amplification
C3(H2O)

Membrane damage
Alternative pathway activation

1. Immune adherence

2. Chemotaxis
   - Phagocytosis
   - Inflammation

3. Immune regulation

4. Bacteriolysis
Inflammatory effects mediated by C5a

Chemotaxis
- Lysosomal enzyme release
- Neutrophil aggregation

Histamin release
- Smooth muscle contraction
- Increased permeability

Cell adhesion
- CR3 (CD11b/18)

Cytokines
- IL-1, IL-6, IL-8, TNF

CR1 and FcR expression

B- and T-cell responses

Reactive oxygen metabolites

Arachidonic acid metabolites (LT, PG)

Platelet activating factor (PAF)
Danger signaling
Complement and \textit{altered self}

- Normal cell
- Apoptotic cell
- Endothelial damage
- Cancer cell
Endothelium and Complement

Intact endothelium
- The only fully complement compatible surface?
  - Blocking DAF/MCP induced spontaneous leakage

Damaged endothelium
- Endothelium is damaged by complement
- Damaged endothelium activates complement
Reasons to analyse complement

• **Complement deficiencies**
  - are associated with certain diseases

• **Complement activation**
  - clinical: reflects ongoing disease processes
  - experimental: animal and *in vitro* models

• **Complement pharmacology**
  - has already reached clinical medicine
CH50 - Total Complement Hemolytic Activity

Detection of complement deficiency

Classical CH50

Sensitized SRBC

Serum

C1 C4 C2

B D P

C3

C5

C6 C7 C8 C9

Lysis (Hb release)

Alternative CH50

RRBC Mg EGTA
Total Complement System Activity

Serum is added to micro-titer wells

- Classical pathway
  - C1qrs
  - C2
  - C3
  - C4
  - C5
  - C6
  - C7
  - C8
  - C9

- Lectin pathway
  - MBL
  - MASP-2
  - C2
  - C3
  - C4
  - C5
  - C6
  - C7
  - C8
  - C9

- Alternative pathway
  - FB
  - FD
  - C3
  - C4
  - C5
  - C6
  - C7
  - C8
  - C9

Components:
- IgM
- Mannan
- LPS
Enzyme immunoassay (EIA) for quantification of TCC (neoepitope)
Complement deposition in tissue

MPGN II in factor H dysfunction
TCC (C5b-9) in glomeruli

Acute Ab-mediated rejection
C4d in peritubular capillaries
Complement in the future

Therapeutic aspects

Eculizumab (Soliris®)

- Paroxysmal nocturnal hemoglobinuria
- GPI-anchor defect (e.g. DAF, CD59)

PNH

C5 → C5a
C5b-9

Biomaterials incompatibility
Platelet storage
Hemodialysis
Cardiopulmonary bypass equipment

COMPLEMENT DISEASES

Acute
- Adult respiratory distress syndrome
- Ischemia-reperfusion injury:
  - Myocardial infarct
  - Skeletal muscle
  - Lung inflammation
- Hyperacute rejection (transplantation)
- Sepsis
- Cardiopulmonary bypass
- Burns, wound healing
- Asthma
- Restenosis
- Multiple organ dysfunction syndrome
- Trauma, hemorrhagic shock
- Guillain-Barré syndrome

Chronic
- Paroxysmal nocturnal hemoglobinuria
- Glomerulonephritis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Infertility
- Alzheimer’s disease
- Organ rejection (transplantation)
- Myasthenia gravis
- Multiple sclerosis

Makrides SC. Pharmacol Rev 1998
Complement in summary