Main functions of the complement system

1. Lysis of microbes (MAC)
2. Opsonization (C3b, C4b, C1q)
3. Generation of an inflammatory reaction (C5a, C3a, C5b-9)
   - mediator release from mast cells
   - contraction of smooth muscle cells
4. Chemotaxis and activation of phagocytes (C5a)
5. Processing of immune complexes (C3b, C4b, CR1)
6. Strengthening the B- and T-cell immune responses
   - natural (endogenous) adjuvant effects via C3d-CD21 and IC3b-CR3

Dual role of complement in the development of immunological inflammation

1. Too much:
   - Causes inflammation and tissue damage
   - (C5a and the membrane attack complex; MAC)

2. Too little:
   - Failure in the clearance of damaged tissue or microbes
   - debris or microbial components persist
   - (auto)immune responses develop

Clearance of apoptotic or injured cells

C1q, C1r, C1s, C2 or C4A-deficiencies
- problem in clearance of debris — SLE, SLE-like sdr
Loss of self-control
-> tissue damage
-> inflammation

Innate Autoreactivity vs. Autoimmunity
- attack against "self" by the innate immune system
- not caused by antibodies or autoreactive T cells
- caused by disturbances in control mechanisms
  - > overactivation or lack of inhibition
Examples:
- complement regulator deficiencies
- autoinflammatory syndromes

Mechanisms of discrimination between self and nonself by complement
1. protective coating by sialic acid and glycosaminoglycans (e.g. glycoporphin-sialic acid on RBCs)
2. Membrane regulators of complement activation
   Complement receptor type 1 (CR1, CD35)
   Membrane cofactor protein (MCP, CD46)
   Decay accelerating factor (DAF, CD55)
   Protectin (MAC inhibitor, CD59)

Failure in control
--> “INNATE AUTOREACTIVITY”
C3b-PNH
  - hereditary angioedema (HAE)
Factor H (Hemminus)
  - dense deposit disease (DDD, MPGN2)
  - partial lipodystrophy (PLD), age-related macular degeneration (AMD)
Factor H (Hemminus)
  - hemolytic uremic syndrome (aHUS)
Factor I
  - hemolytic uremic syndrome (aHUS)
CD46 (MCP)
  - hemolytic uremic syndrome (aHUS)
CD59
  - paroxysmal nocturnal hemoglobinuria (PNH)
Complement factor H

- soluble plasma protein
- consists of 20 short consensus repeat (SCR, "sushi") domains
- inhibitor of the alternative pathway of complement

Binding sites:
- ++ Heparin
- C3b
- CRP

Cleavage of complement C3

C3 convertase Factor I Factor H

Dense Deposit Disease
(Membranoproliferative glomerulonephritis type 2)

1. Caused by total deficiency or functional blocking of the N-terminus of factor H (SCR1-5) (or by anti-C3bB = C3 Nef or by anti-H antibody)
2. Glomerular damage is due to continuous activation of the alternative pathway
3. Leads to C3 & MAC deposition and dense deposits on GBM

Discrimination between activators and nonactvators ("nonself-self")

X = any surface, A = activator, NA = nonactivator

Factor H and AMD

- Science Vol. 308 15 April 2005

CRP = C-reactive protein
Age-related Macular Degeneration

- The most common cause of blindness in the developed countries in people over 65
- Loss of central vision
- E.g. reading, driving and recognizing faces impossible in advanced AMD
- Associated with a SNP (1277T→C) that leads to one amino acid change: Y402H in SCR7 of FH
- No curative treatment

Complement factor H and hemolytic uremic syndrome

1. Familial HUS: a non-diarrheal form
2. Microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure
3. Thrombotic microangiopathy due to vessel wall thickening and swelling and detachment of endothelial cells from the basement membrane
4. Caused by point mutations in MCP, F1, (FB) or in the C-terminus of FH (SCR19-20) -> dysfunctional or low levels of factor H

From mutations to therapy

- A 1-year-old boy, his 16-year-old aunt and a 19-year old man, all with HUS and end-stage renal disease (heterozygous FH R1215Q mutation)
- Successful recovery in all 3 cases
Protected "self" (nonactivating surface)

Polyanions (glycosaminoglycans, sialic acid, phosphorolipids)

Loss of protection -> attack against self tissues (innate autoreactivity)

Factor H
1) Inhibits factor B binding to C3b.
2) Accelerates the decay of C3bBb.
3) Collector for factor I in cleaving C3b to iC3b
   -> Inhibition of phagocyte and killing by MAC

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