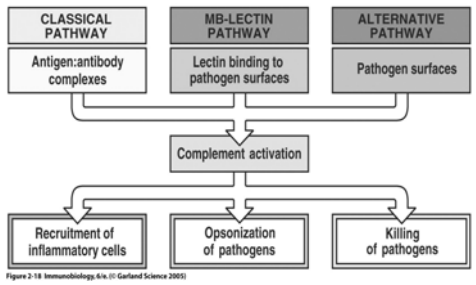
Functions of Complement

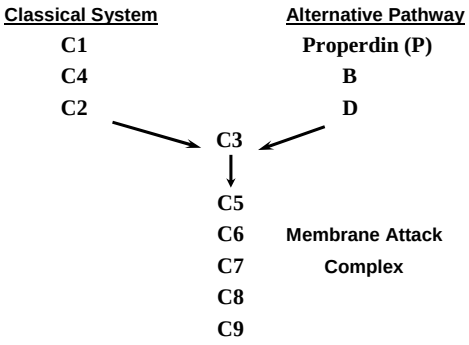
A. Host Defense

B. Disposal of Waste

C. Regulation of the Immune Response



Complement Cascades



Nomenclature

- Inactive Protein - C3
- Cleaved Products - C3a, C3b, iC3b, C3dg (many have enzymatic and biologic activity)
- Enzyme Complexes
- Alternative Pathway C3 convertase - C3bBb
- Classical Pathway C3 Convertase – C4bC2b

Alternative Pathway

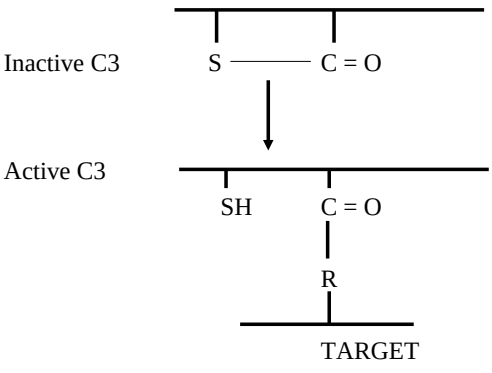
C3

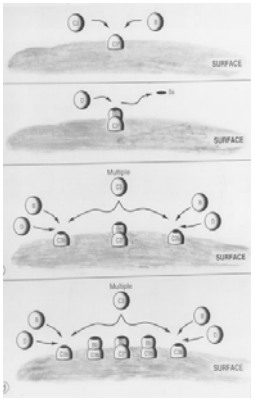
B

D

Properdin (P)

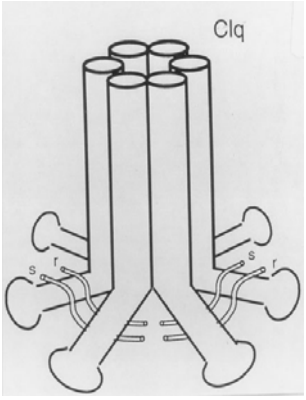
(P stabilizes the complex formed by C3b and Bb)

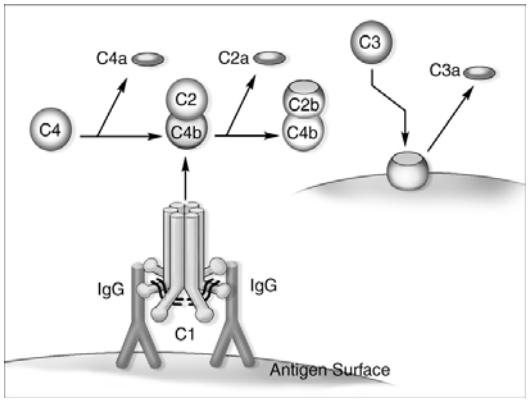




Gene Duplication

Alternative		Classical
		C1
C3	→	C4
B	→	C2
		C3





Concerning C2 Nomenclature

There is an argument about nomenclature

Classicists and Abbas – big piece C2a, little piece C2b (the original nomenclature)

Revisionists and Janeway – big piece C2b, little piece C2a (to be consistent with the rest of the complement notational conventions)

Absolutely not on the exam

Activation of Complement- The Lectin Pathway

- A lectin is a molecule that binds to carbohydrate structures
- A collectin (like C1q or Mannose Binding Protein) is a lectin with collagen like features
- It is simplistic to think of each "pathway" as acting in isolation. Thus, once the classical pathway has produced some C3b, these C3b molecules produce more C3b using the alternative pathway
- C-reactive protein (CRP) – An "acute phase" protein produced by the liver, binds to bacterial cell wall lipopolysaccharides. C1q then binds to CRP and thus activates complement without involving antibodies. The test for CRP is frequently ordered in clinical situations where inflammation is suspected

Mannose Binding Lectin (MBL)

- MBL – A collectin similar in structure to C1q first binds to mannose on bacterial cell walls. It then binds MASP 1,2 or 3, (Mannose binding lectin – Associated Serine Proteases).These can then activate C4 and C2 and thus the classical pathway without involving antibodies.
- Deficiency in MBL is associated with increased susceptibility to bacterial infections

Mannose Binding Lectin

↓

MBL, MASP1, MASP2

C4

C2

↓

C3

Complement Receptors

Receptor	CD Designation	Ligands
CR1	CD35	C3b
CR2	CD21	C3d
CR3	CD11b/CD18	iC3b
CR4	CD11c/CD18	iC3b

Molecules That Regulate Complement

- MCP (Membrane Cofactor Protein, CD46) and DAF (Decay Accelerating Factor, CD55) - Cell surface molecules that inhibit C3b
- Factor H and C4b binding protein – Fluid phase molecules that bind C3b and C4b respectively
- Factor I – Fluid phase molecule that cleaves C3b when it is bound to Factor H, CR1 or MCP
- CD 59 (membrane bound) and Plasma S Protein both interfere with the Membrane Attack Complex

Regulators of Complement Activation (RCA) Family (interact with C3 and/or C4)

CR1
CR2
DAF
MCP
→ Membrane-bound

Factor H
C4BP
→ Fluid phase

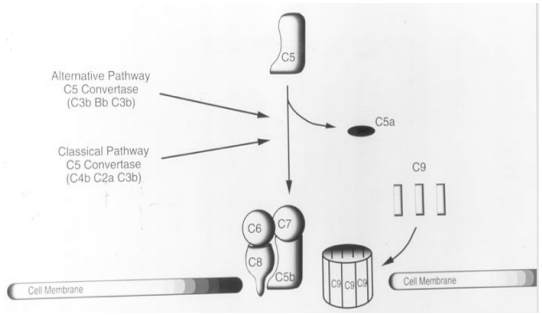
C3
↓ ← Alternative and Classical Pathway
C3b + C3a
↓ ← C3 convertases
iC3b
↓ ← Factor I + Factor H or CR1 or MCP
iC3b + C3f
↓ ← Factor I + CR1
C3c +C3dg
↓ ← Serum proteases
C3d + C3g
Serum Proteases

Host Defense

1) Lysis of Pathogens

2) Induction of Inflammation

3) Opsonization



Host Defense

1) Lysis of Pathogens

2) Induction of Inflammation

3) Opsonization

<u>C5a, C3a, C4a</u>

Smooth muscle contraction
Increased vascular permeability
C3a, C5a induce vascular adhesion molecules
C5a activates leukocytes and induces chemotaxis
Cause mast cell mediator release

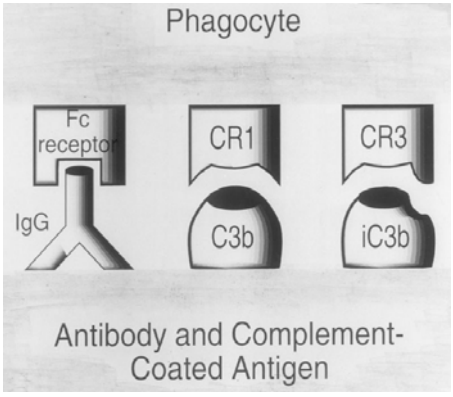
Massive mediator release causes syndrome similar to anaphylaxis

Host Defense

1) Lysis of Pathogens

2) Induction of Inflammation

3) Opsonization



β_2 Integrins

Names	CD	Ligands
LFA -1	CD11a/CD18	ICAMs
CR3 (Mac-1)	CD11b/CD18	iC3b, ICAMs, many others
CR4 (p150, 95)	CD11c/CD18	C3b, iC3b

Leukocyte Adhesion Deficiency (LAD)

Absence of CD18
No LFA-1, CR3, CR4
Phagocytosis Impaired

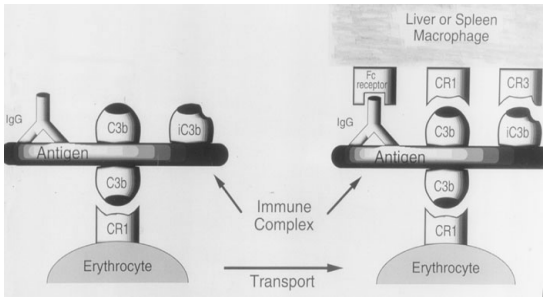
Patients susceptible to bacterial infections

Functions of Complement

Disposal of Waste

Immune Complex Removal

Apoptotic Cell Debris Removal



Functions of Complement

Disposal of Waste

C1q helps removal of apoptotic cell debris
(Antibody not required)

Failure in C1q deficiency
(1) Increased deposition of debris in kidney
(2) Possibly stimulates production of autoantibodies

Functions of Complement

A. Host Defense

B. Disposal of Waste

C. Regulation of the Immune Response

Immune Regulation by C3dg

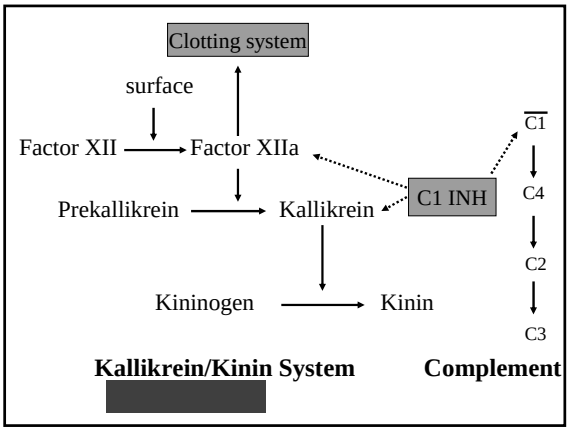
C3dg bound to antigen binds to CR2

(1) Stimulates B cells

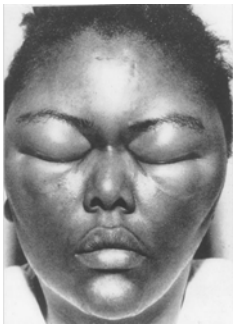
(2) Epstein-Barr Virus (EBV) uses CR2 to enter B cells

Disorders of the Complement System

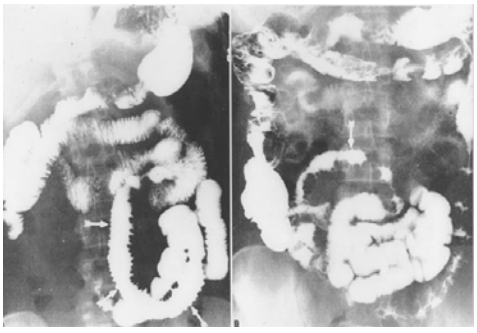
Hereditary Angioneurotic Edema



Hereditary Angioneurotic Edema



Hereditary Angioneurotic Edema



Paroxysmal Nocturnal Hemoglobinuria

1) Stem cell clone arises that does not have DAF and CD59
2) Red cells and platelets cannot repair damage caused by unregulated complement
3) Patients suffer hemolysis and thrombosis

Factors H & I Deficiency

1) Consumption of C3

2) Acquired C3 deficiency

3) Susceptibility of patients to bacterial infection

Complement Deficiencies

C1q, C1r, C1s, C2, C4	Markedly increased incidence of autoimmune disease Moderate increased incidence of pyogenic infections
H, I, C3	Increased incidence of pyogenic infections. Moderately increased incidence of autoimmune disease
Properdin, Factor D, C6, C7, C8, C9	Increased incidence of *Neisseria* infection
CR3, CR4	Increased incidence of pyogenic infection.
C1 INH	Hereditary angioedema
DAF, CD59	Paroxysmal nocturnal hemoglobinuria

Complement Tests

- Tests that simply measure the presence of a protein
- Tests that measure whether a protein (e.g. C1 inhibitor) or an entire system is functional
- Total Hemolytic Complement (CH_{50}) is a commonly ordered test that measures the combined function of the classical and membrane attack systems

Total Hemolytic Complement Measurement

Method

Mix **RBC, Anti-RBC, Serial dilutions of serum**

Results

Serum Dilutions:	**1/50**	**1/100**	**1/150**	**1/200**
Hemolysis:	**100%**	**100%**	**50%**	**20%**

CH_{50} = 150 (Reciprocal of 1/150)

Measurement of Complement

Systemic lupus erythematosis	CH_{50} tends to fall
Hereditary angioedema (HAE)	C1 INH levels low
C4 Deficiency (also other deficiencies of the classical pathway and the membrane attack complex)	CH_{50} essentially zero If zero CH_{50} of zero is noted in patients with autoimmune disease, check for deficiencies in the classical pathway or membrane attack complex.
Recurrent *Neisseria* Infections	Properdin, Factor D, C5, C6, C7, C8, C9 (Any of these can be absent)