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The Complement System in Human Disease

M1 – Immunology Sequence
Joseph Fantone, MD

THE COMPLEMENT SYSTEM IN **HUMAN DISEASE**

- I. LEARNING OUTCOMES: To Understand the**
- role of complement in inflammation and the effects of specific complement deficiencies on patients.
 - mechanisms by which the complement system is activated and regulated.
 - effector molecules of complement activation and their biologic function.
 - role of complement in bacterial clearance and lysis.
 - use of plasma CH50 levels in the assessment of disease processes.

COMPLEMENT SYSTEM

- The learning outcomes for this topic will be attained by viewing a self-directed learning module supplemented by the syllabus.

<http://www.umich.edu/~projbnb/imm/complement.swf>

- It is expected that the student will view the video prior to the lecture presentation on phagocytic cells (2/10: 9-10:00am).
- Any questions will be addressed by Dr. Fantone prior to and after the Phagocytic Cell lecture

II. Why study the complement system?

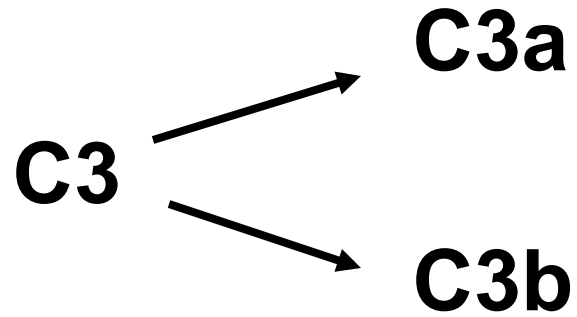
- Innate & Adaptive Immunity
- Infection
- Inflammation
- Cell lysis
- Immune complex disease
- Autoimmune disease

III. Definition: Complement consists of more than 20 proteins present in plasma and on cell surfaces that interact with each other to produce biologically active inflammatory mediators that promote cell and tissue injury

Nomenclature:

a. the first component of complement is named C1 (etc.) other components are designated by capital letters and names: Factor B, Properdin

b. when cleaved: fragments of complement components are designated by small letters (e.g. C3a and C3b)



Factor B \longrightarrow **Ba + Bb**

Factor H

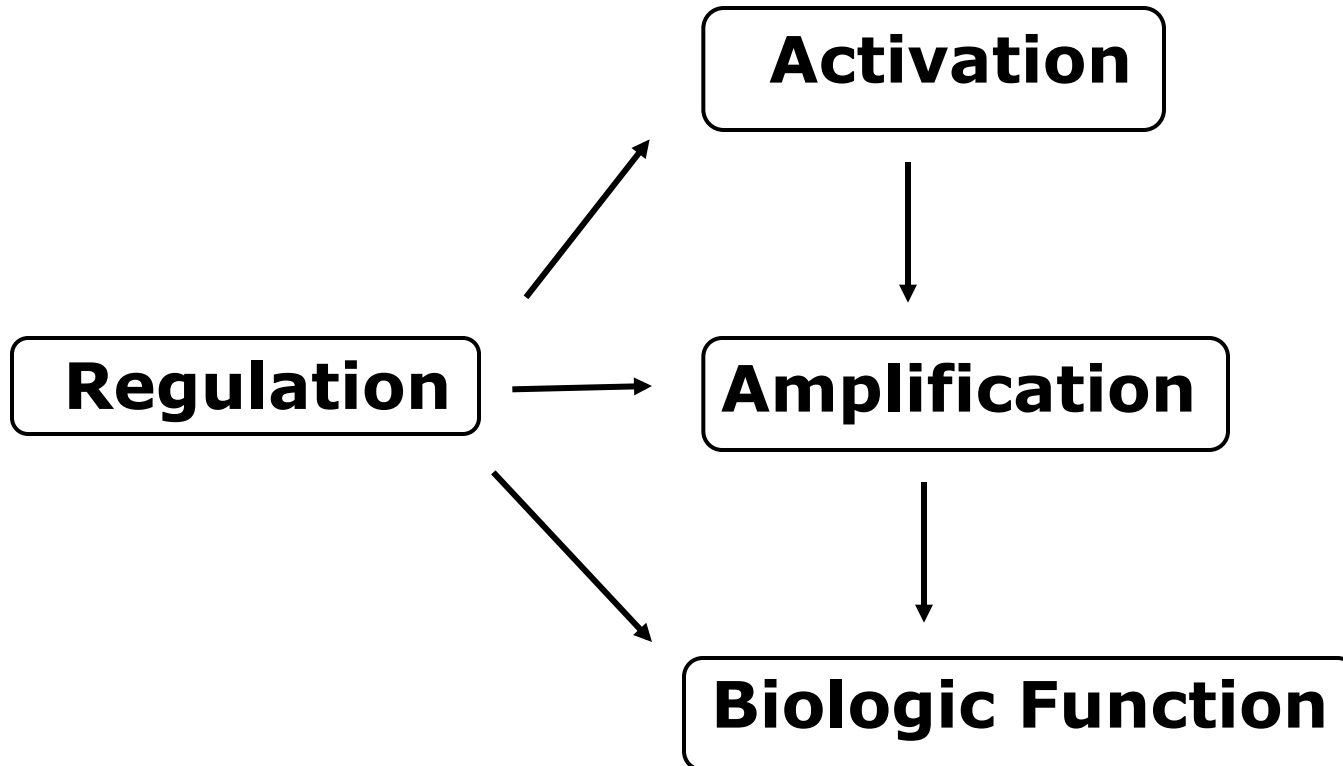
Factor I

IV. Summary of Complement Pathways

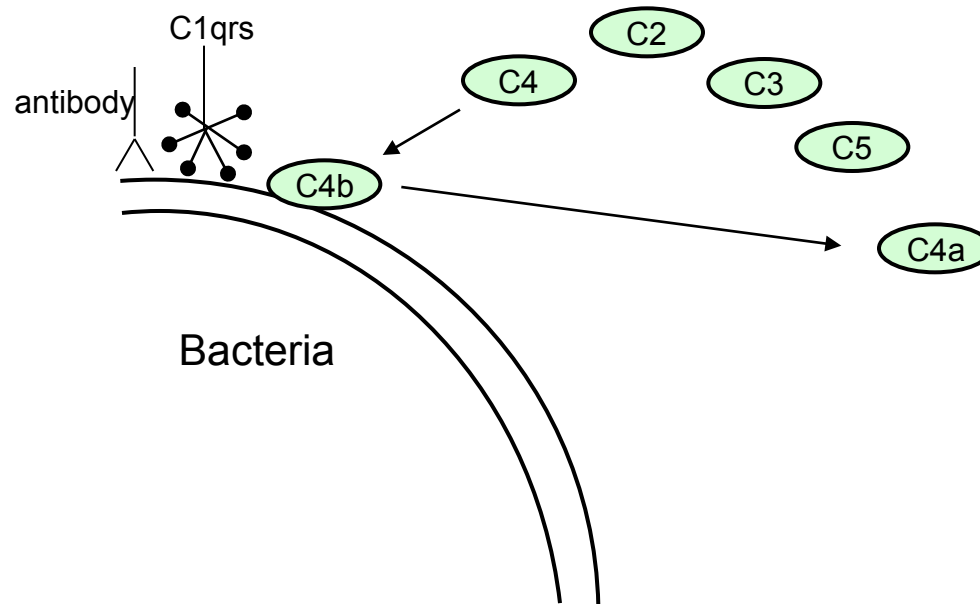
3 pathways for activation:

1. classical: most specific (antibody dependent activation, binds C1)
2. lectin binding: some specificity (mannose binding protein, binds C4)
3. alternative: most primitive (non-specific, auto-activation of C3)

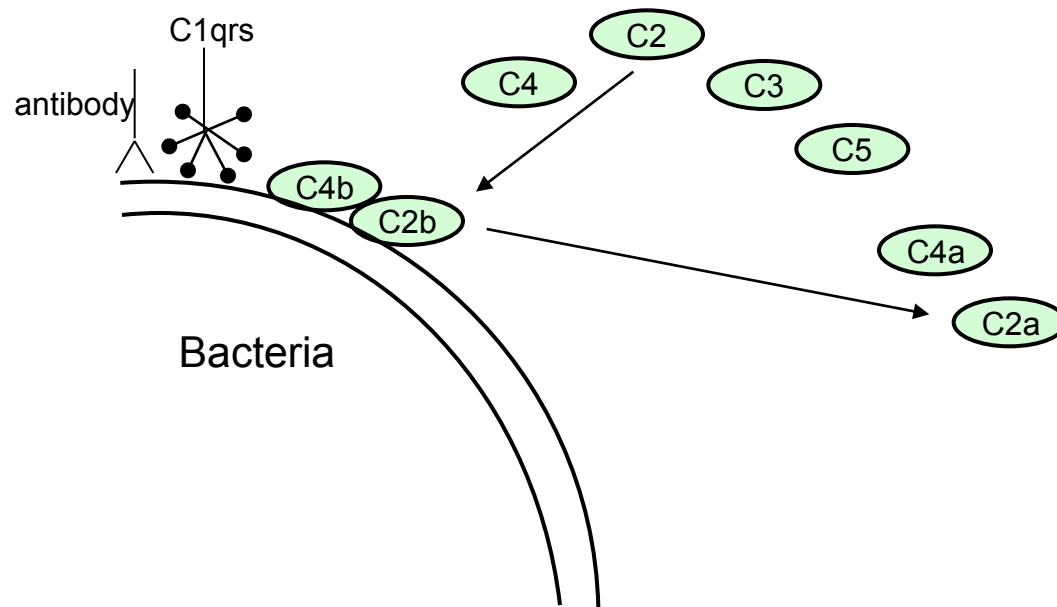
Complement System



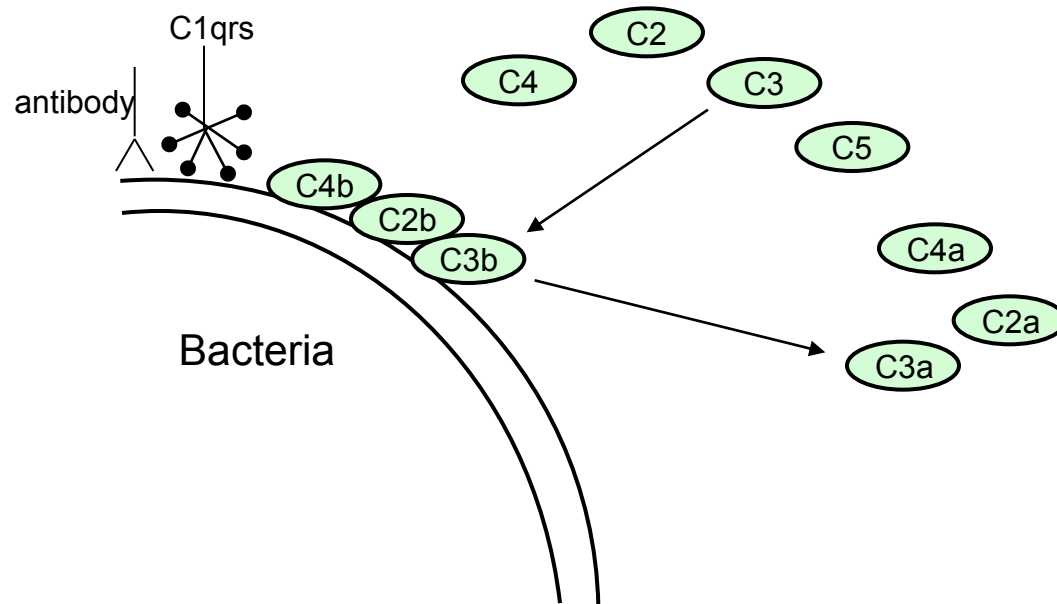
Classical Complement Pathway



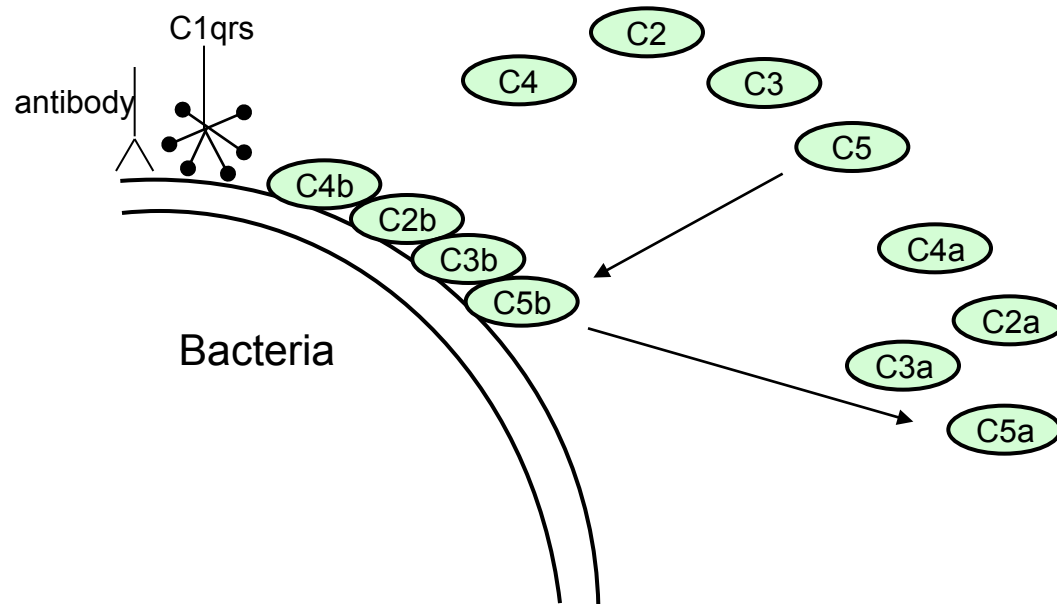
Classical Complement Pathway



Classical Complement Pathway

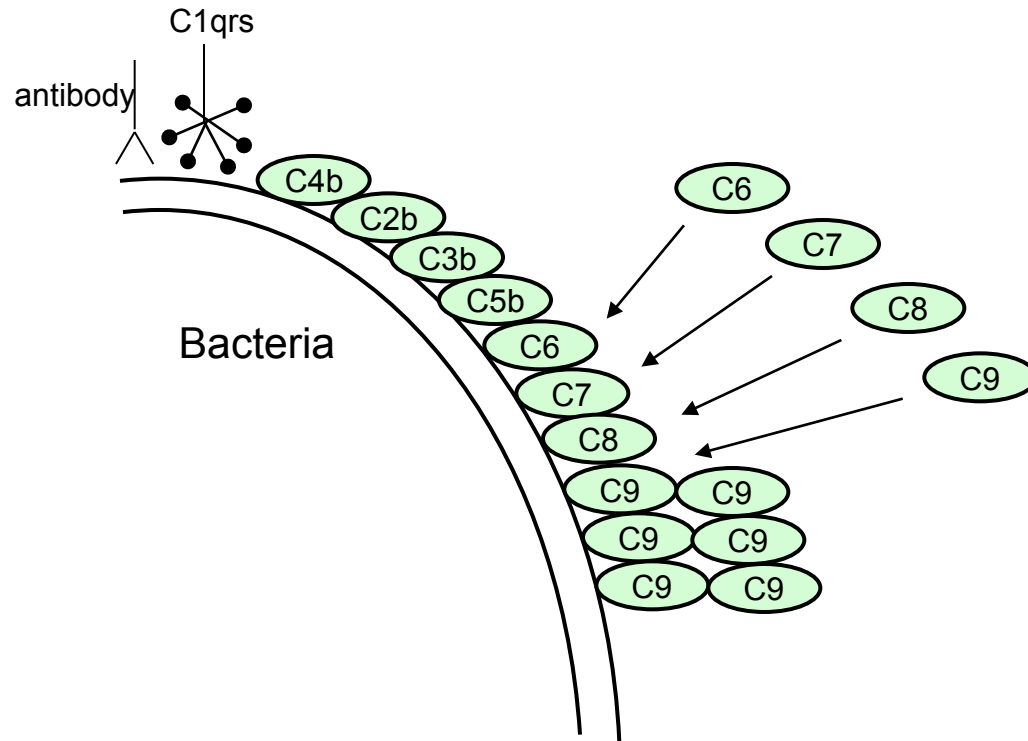


Classical Complement Pathway



Animation complete

Classical Complement Pathway



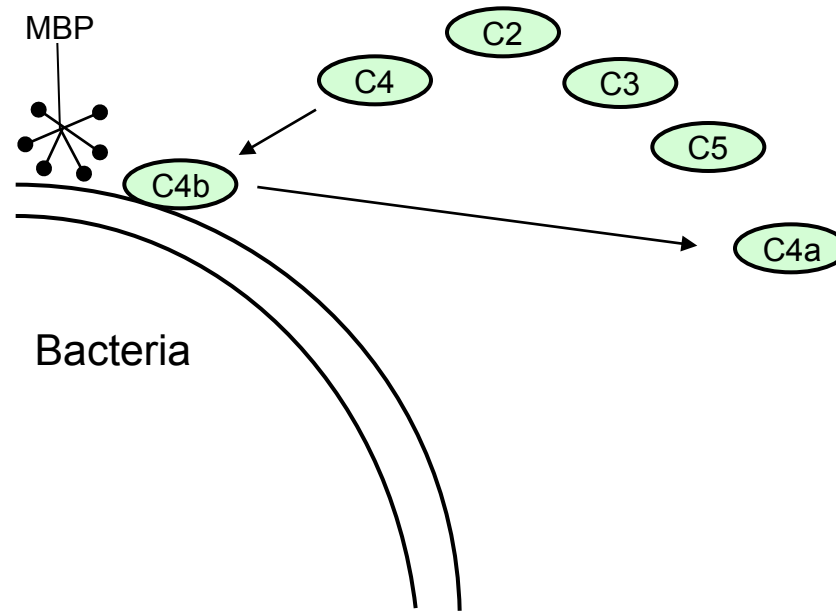
Animation complete

V. Amplification:

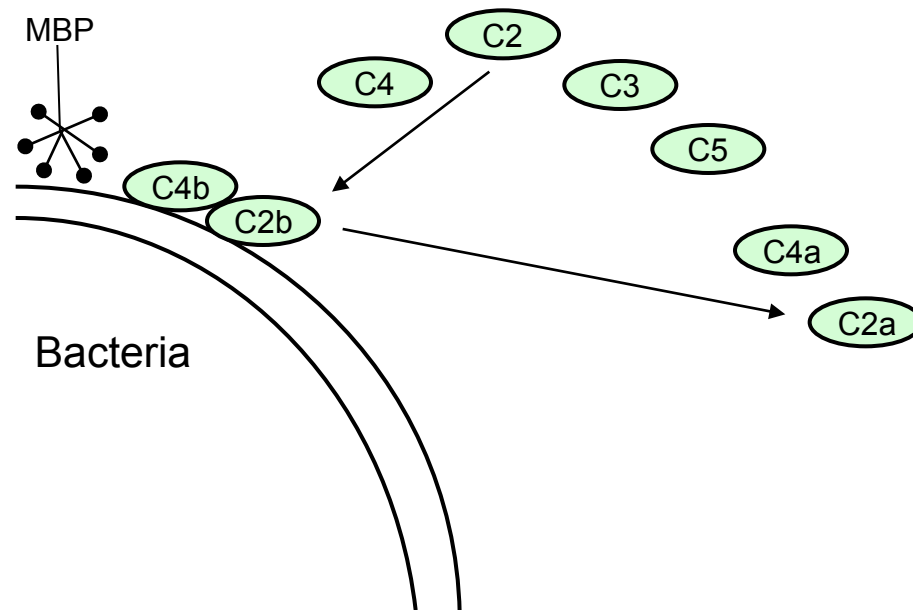
C3 convertase: binds and cleaves multiple C3 molecules on surface to form C3b +C3a

- classical: C4b2b**
- alternative: C3bBb**

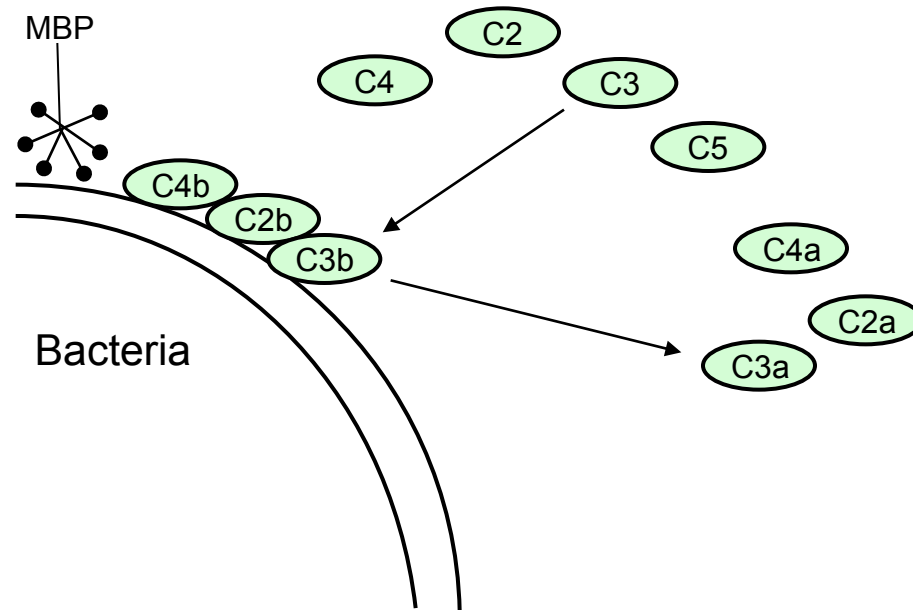
Lectin Binding Complement Pathway



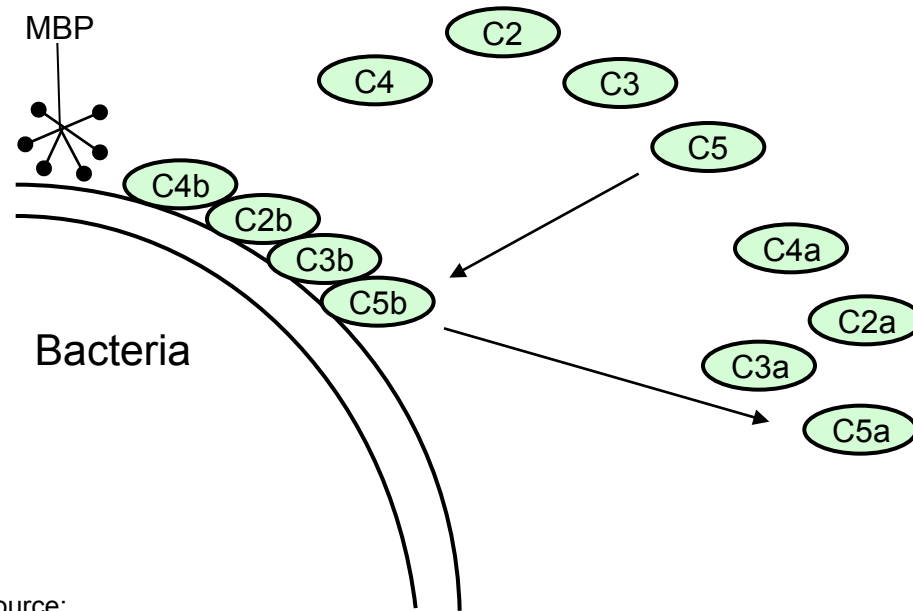
Lectin Binding Complement Pathway



Lectin Binding Complement Pathway



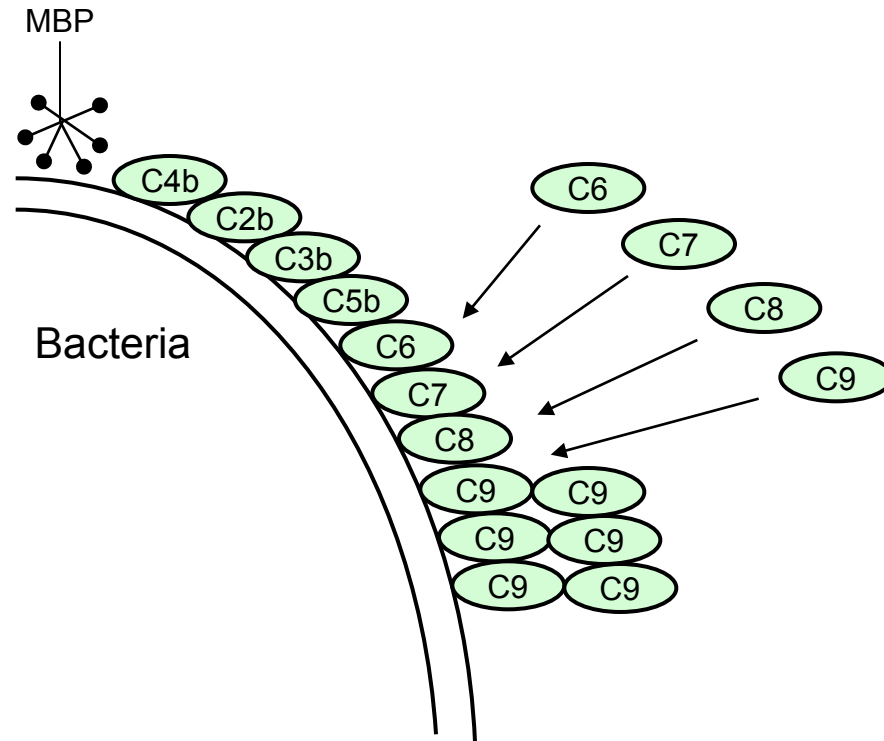
Lectin Binding Complement Pathway



Source:
Undetermined

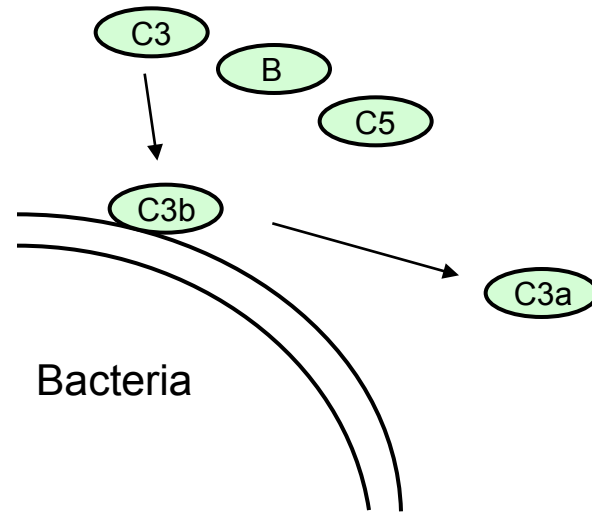
Animation complete

Lectin Binding Complement Pathway

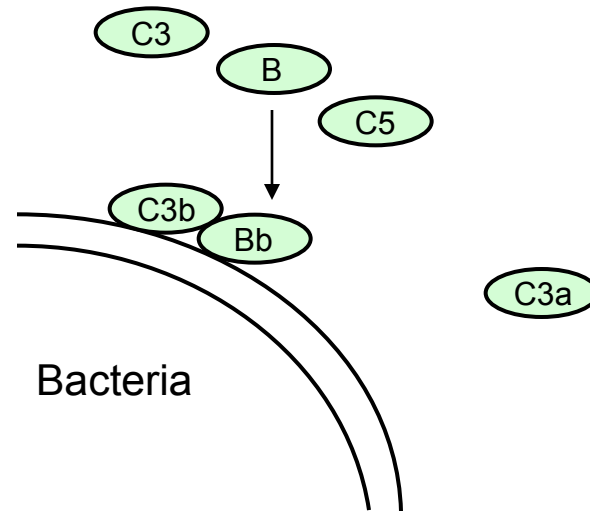


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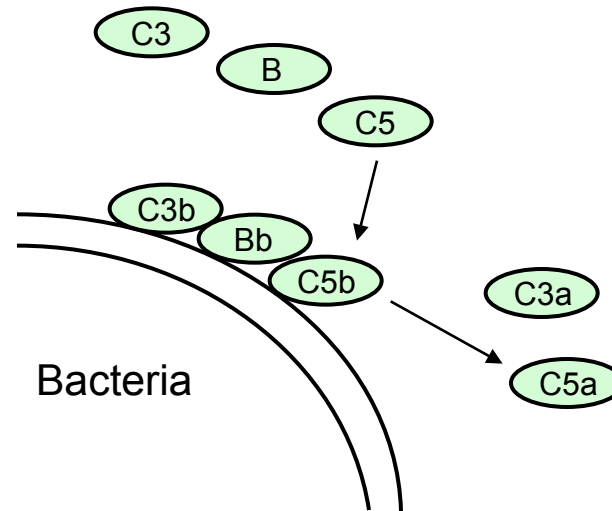
Alternative Complement Pathway



Alternative Complement Pathway

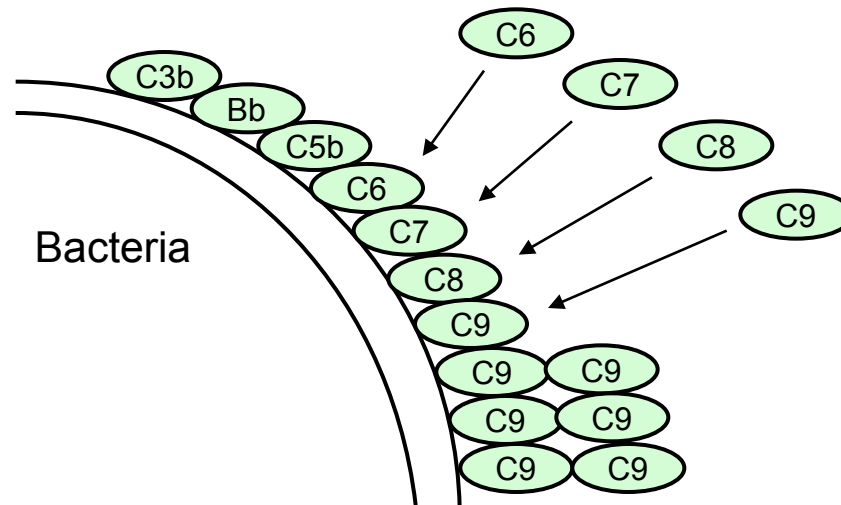


Alternative Complement Pathway



Animation complete

Alternative Complement Pathway

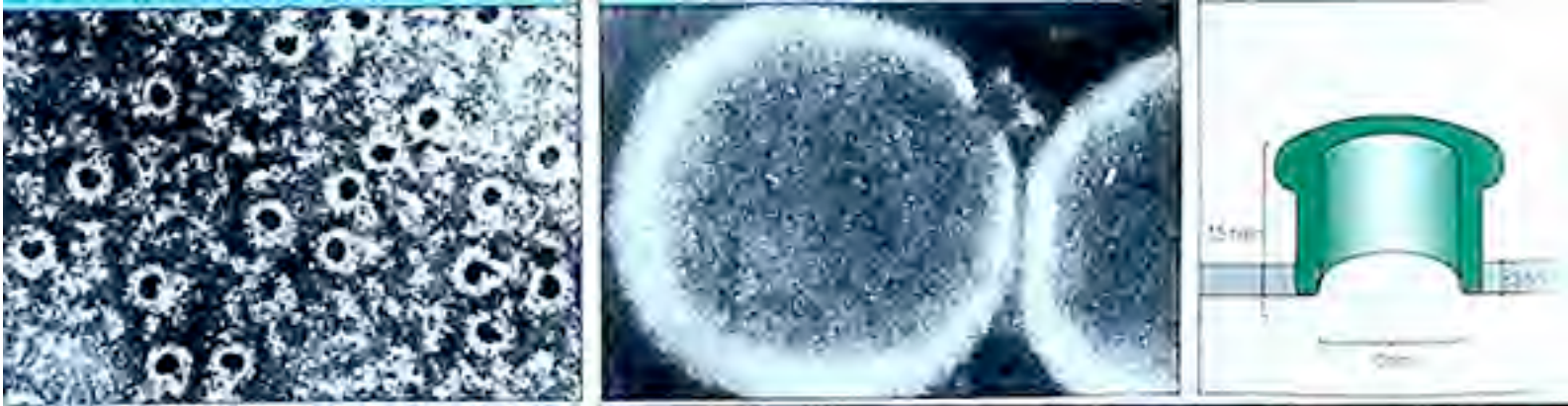


Animation complete

VI. Biologic Function:

- anaphylatoxins: C3a and C5a: mast cell degranulation
 - smooth muscle contraction
 - mast cell degranulation → mediator release (histamine, leukotrienes)
 - vascular changes: dilation, increased permeability (edema)
 - C5a also leukocyte adhesion and chemotaxis (recruitment)
- opsonization: C3b, C3bi, C3d: (binding to complement receptors and enhanced phagocytosis by neutrophils and macrophages)
- clearance of circulating immune complexes
- membrane attack complex: C5b-C9 (cell lysis)

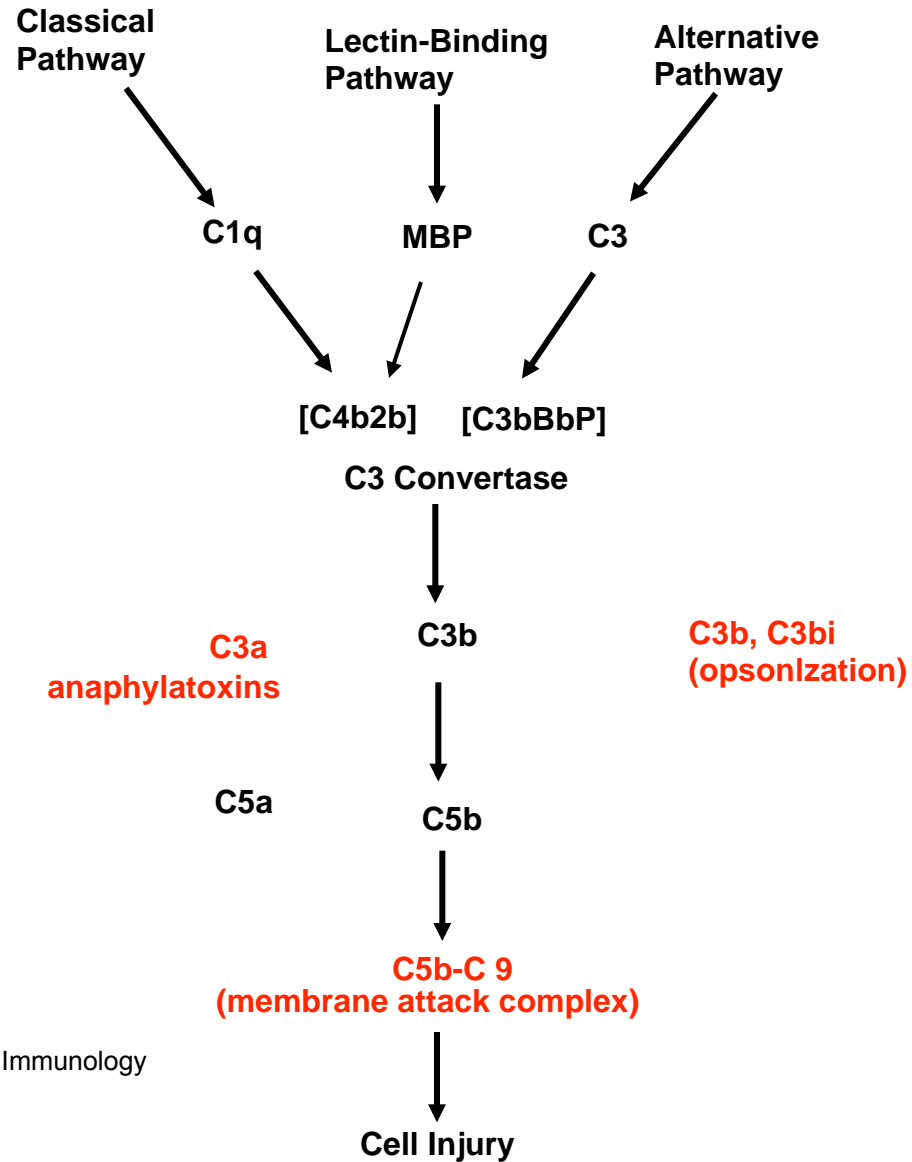
MAC PORES



PD-INEL

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SUMMARY OF COMPLEMENT ACTIVATION



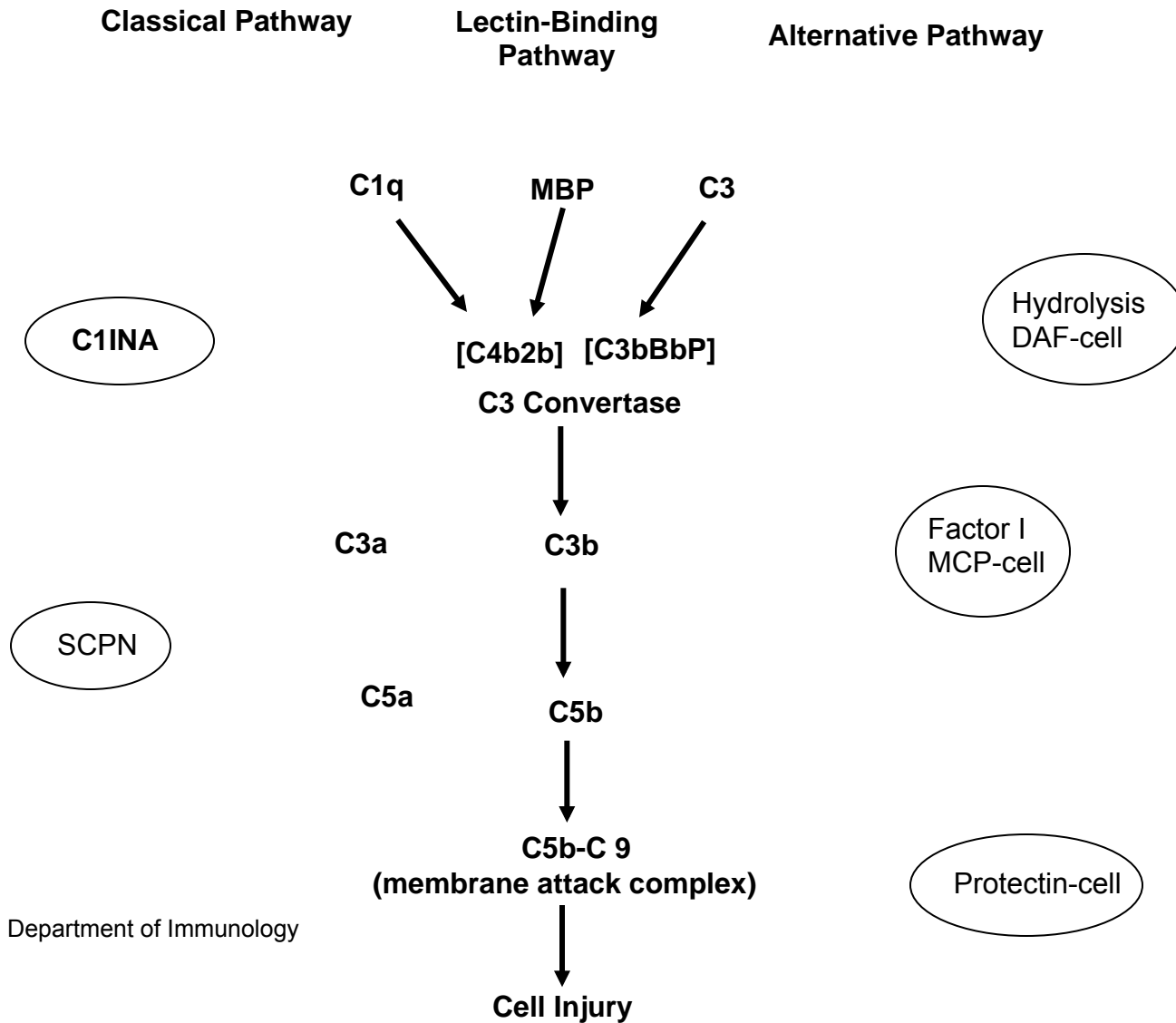
VII. Regulation:

- Inhibit activation: classical pathway
 - C1 inhibitor (C1INA): plasma protein
- spontaneous decay (hydrolysis) of C3 convertases:
- inhibit C3 convertase:
 - Plasma proteins: Factor I
 - Cell membrane proteins:
 - decay accelerating factor (DAF):
 - membrane co-factor protein (MCP):

VII. Regulation

- Inactivate anaphylatoxins: cleave C3a and C5a
 - serum carboxypeptidase N (SCPN):
- Inhibit MAC:
 - Protectin (CD59): cell associated protein

SUMMARY OF COMPLEMENT ACTIVATION



VIII. Complement Deficiencies:

- early components: auto-immune disease
- middle and late components: pyogenic bacterial and nisseria infections
- most common congenital deficiency: C2
- C1INA deficiency: hereditary angioedema
- DAF deficiency: paroxysmal nocturnal hemoglobinuria

IX. Clinical Laboratory Testing

A. Serum complement hemolytic activity:

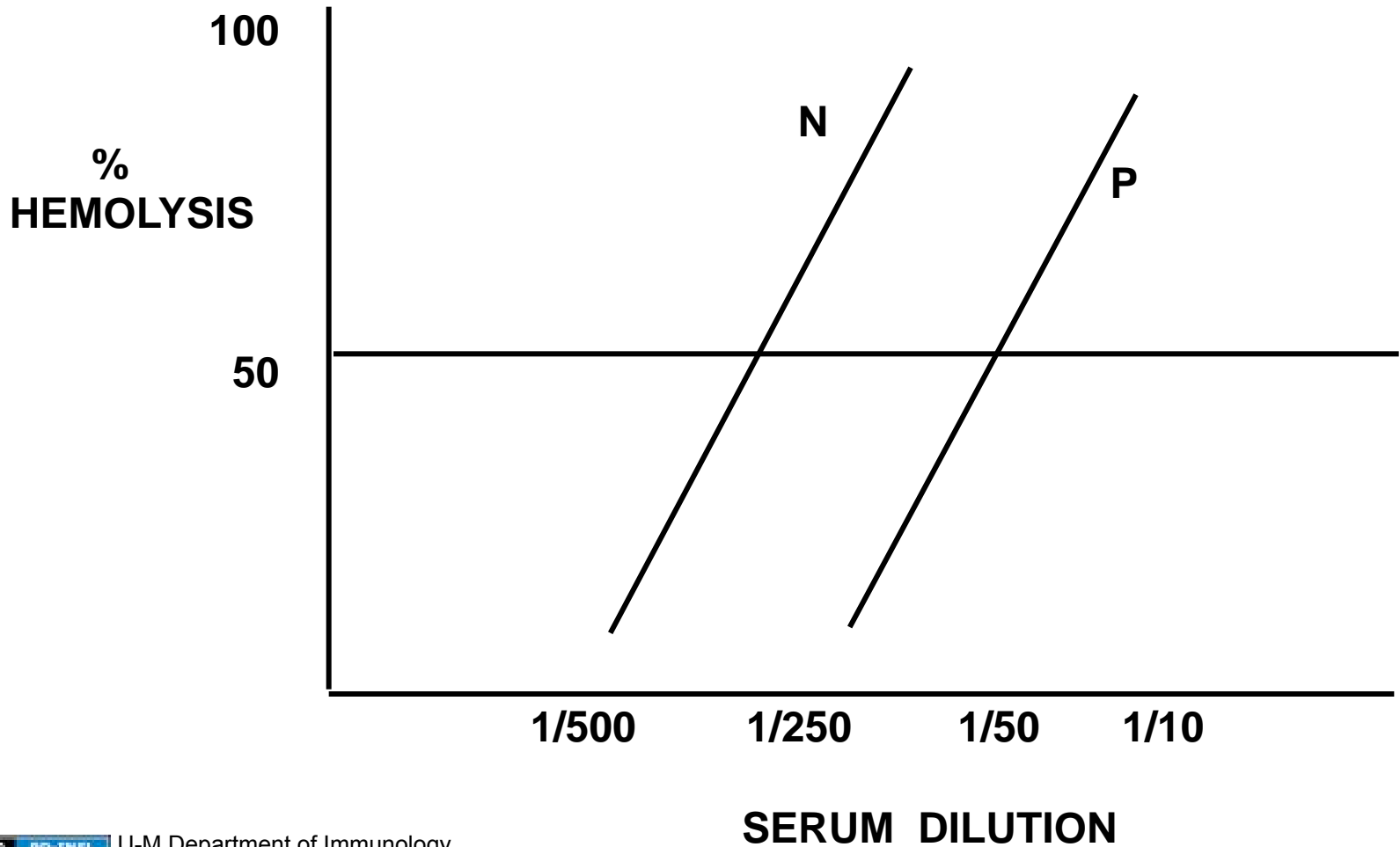
CH50 (serum dilution at which 50% hemolysis occurs)

if low = complement deficiency:

- acquired vs. congenital
- classical vs. alternative pathway defect

B. Individual Components

RBC + AB + SERUM
HEMOLYSIS



Case A: A 23yo man complains of fever (102°F), headache, neck stiffness and fatigue of 2 days duration. Lumbar puncture shows increased pressure with cloudy cerebrospinal fluid containing large numbers of neutrophils, increased protein, decreased glucose and gram negative diplococci. Laboratory studies show C7 (7th component of complement) levels at 18% normal and normal levels of C2, C3 and C5. The patient recovers after institution of intravenous antibiotic therapy.

Case A: Why would this patient be at increased risk for developing bacterial meningitis?

What is the relationship among the three pathways of complement activation and bacterial clearance?

Would a defect in C2 alone place a patient at increased risk of developing bacterial meningitis? Explain.

Case B: A 14yo girl has a long history of excessive swelling after mild traumatic injury. During the past 2 years she has complained of 7 episodes of intermittent abdominal pain sometimes accompanied with watery diarrhea. Laboratory tests show decreased levels of C4 and normal C3 levels. C1 inhibitor levels are 20% of normal.

What pathologic changes would explain this patient's symptoms?

What is the effect of defective C1 inhibitor levels on complement system regulation?

What other inflammatory mediator systems are affected by C1 inhibitor?

Why are these patients not at significant risk for bacterial infection?

Complement Cases

Case A:

Diagnosis: acute bacterial meningitis secondary to deficiency of C7

All three pathways can be activated and the bacteria can be opsonized with C3b and its derivatives: however, the deficiency in C7 results in an inability to assemble the membrane attack complex (MAC) and cause target cell (bacterial) injury

Defects in the early complement components are more frequently associated with the development of autoimmune syndromes (e.g. systemic lupus erythematosus, SLE). This is associated with a failure to clear immune complexes.

In C2 deficiency, the alternative complement pathway remains functional, target cells can still be opsonized with C3b and the MAC formed.

Case B:

The patient's symptoms are the result of increased vascular permeability changes leading to soft tissue swelling and diarrhea.

In the absence of C1 inhibitor there is spontaneous activation of the classical complement pathway with cleavage of C4 and C2. Since there is no target cell surface for complement binding, C3 cleavage does not occur to any significant degree and if some C3b is formed, it undergoes spontaneous hydrolysis –

The C2a and its subsequent products can cause vascular permeability changes. Also, C1 inhibitor interacts with the kallikrein-kinin mediator system. A deficiency in this inhibitor also results in increased kinin formation (e.g. bradykinin), which also promotes vascular permeability changes.

These patients (even if C2 and C4 are depleted) have an intact alternative complement pathway.

Additional References:

Complement:

Kumar, Abas, and Fausto: Pathologic Basis of Disease (7th ed.) pages 64-67.

Additional Source Information

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