COMPLEMENT DEFICIENCIES

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IDF Lunch & Learn

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UNC HEALTH CARE
Children's

Disclosures

- I have relationships with the following commercial entities:
  - Consulting or Speaker Bureau: Pharming Healthcare, Inc., Enzyvant Therapeutics, Inc.
  - Research/Clinical Trials: AbbVie, Amgen, Bristol-Myers Squibb, Janssen

Objectives

- Provide an overview of complement and its important functions, including defense against infection
- Discuss studies available for the evaluation of the complement system
- Review complement deficiencies and their management

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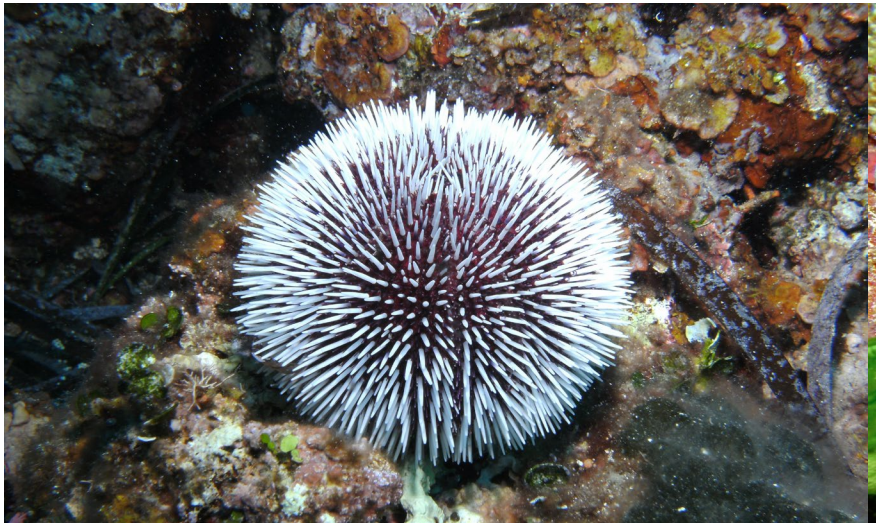
The Complement System

- Major component of the innate immune system
- Also an important helper in humoral immunity
- Collection of more than 30 proteins
- Generally produced by the liver



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https://commons.wikimedia.org/wiki/File:Sea_Squirt_(Didemnum_molle)_(6059268666).jpg

The Complement System

- Normally circulate in a functionally inactive precursor form or “zymogen”
- Activated through a sequence of triggered, enzymatic reactions

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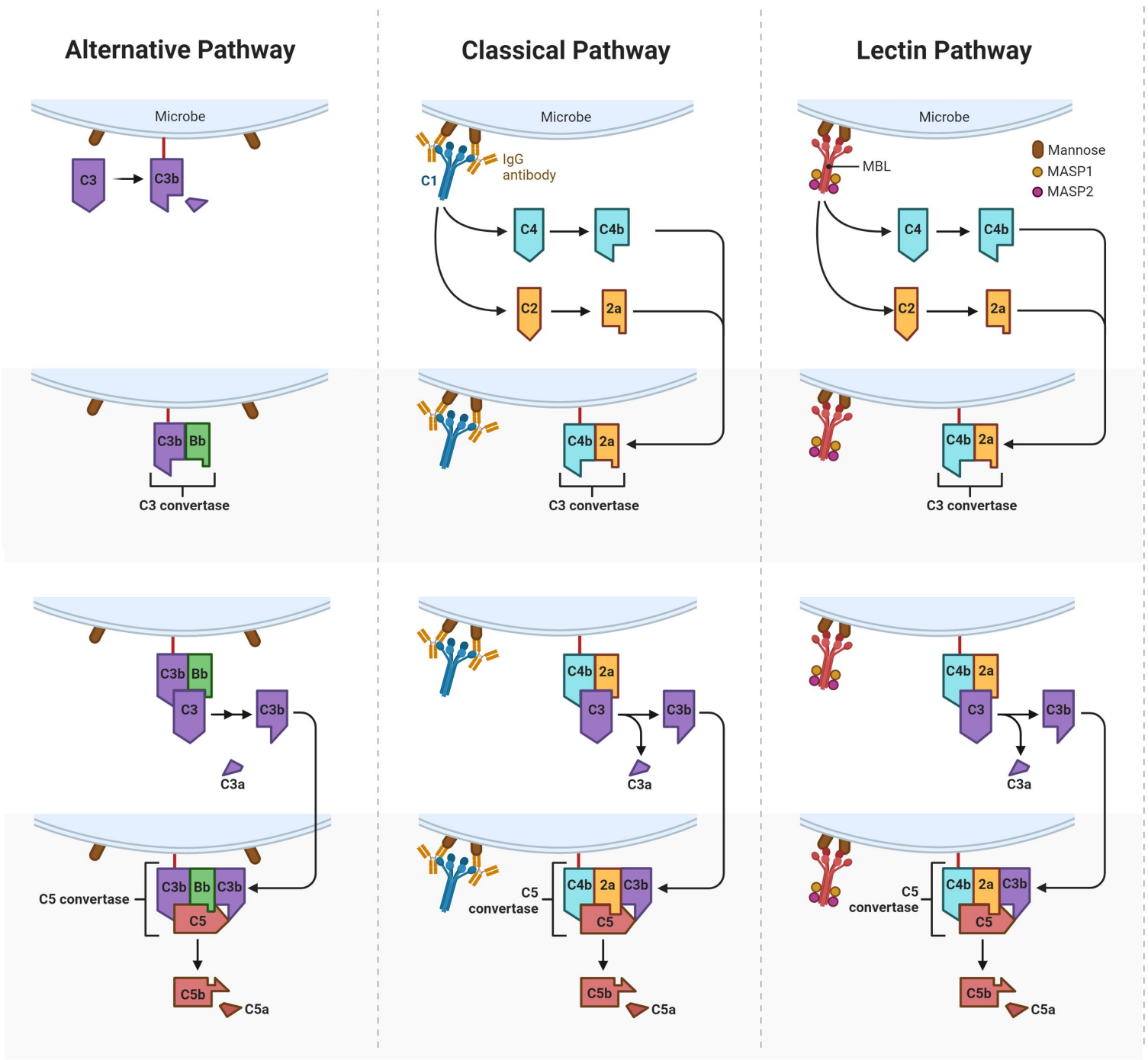

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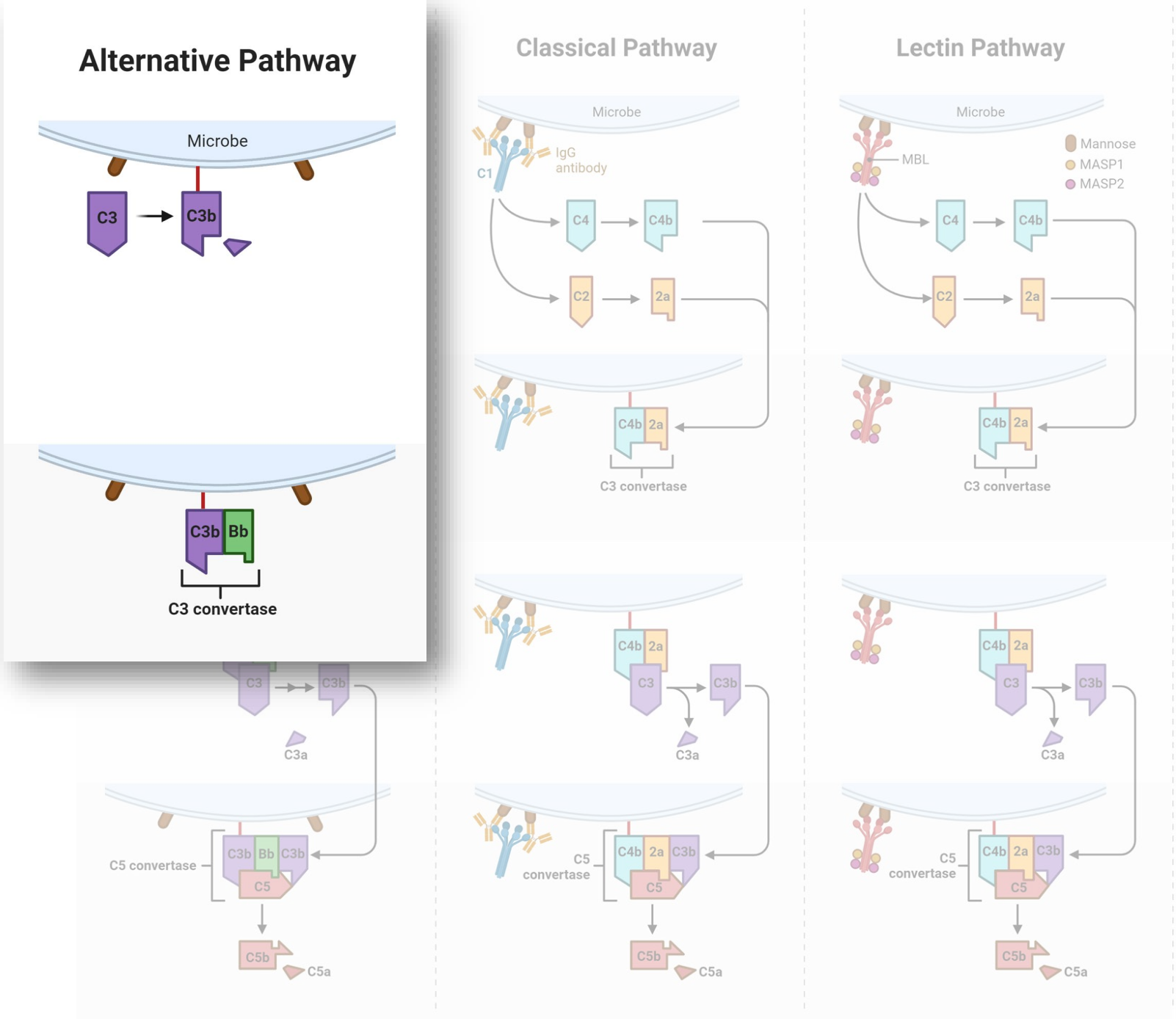

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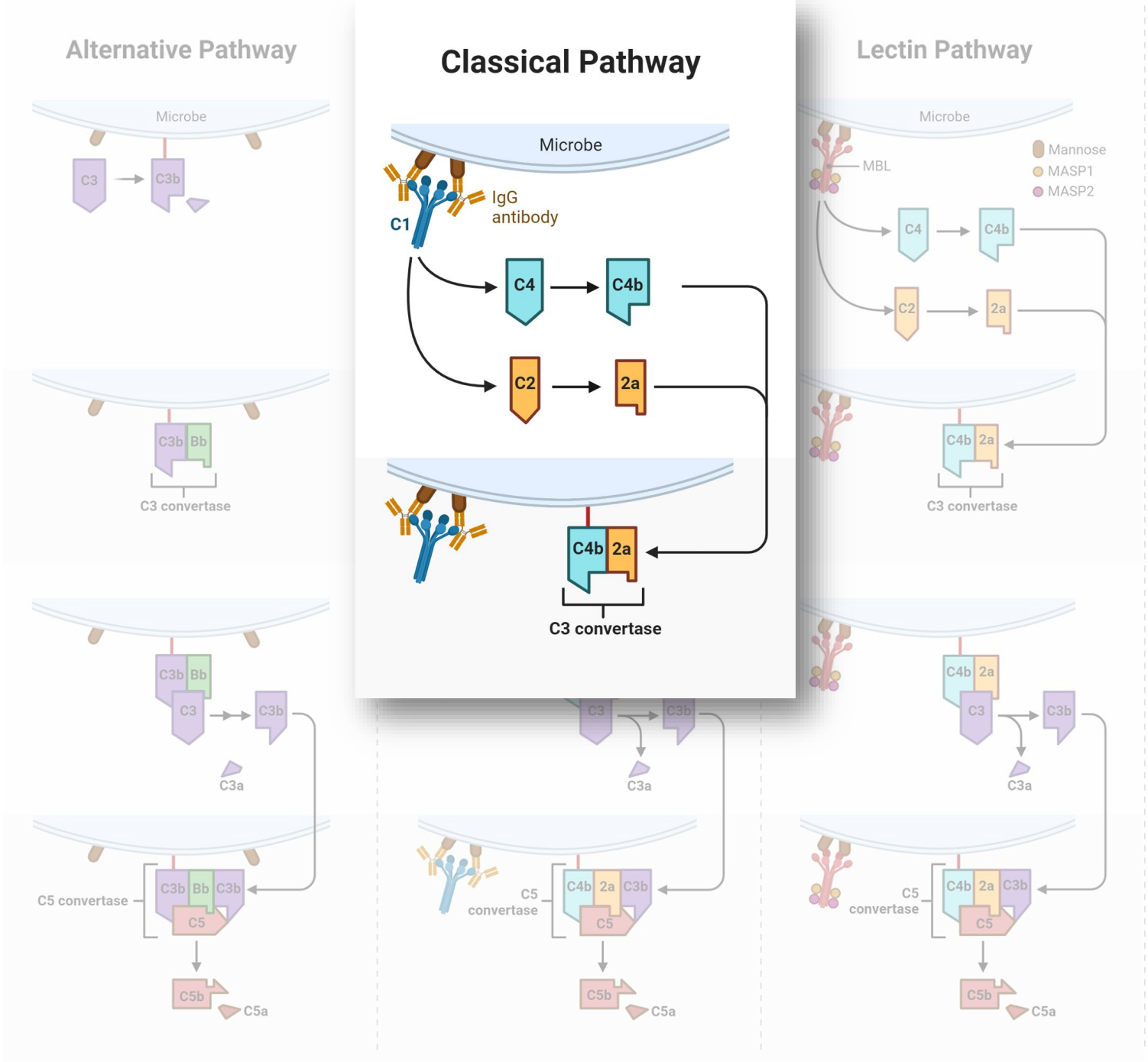

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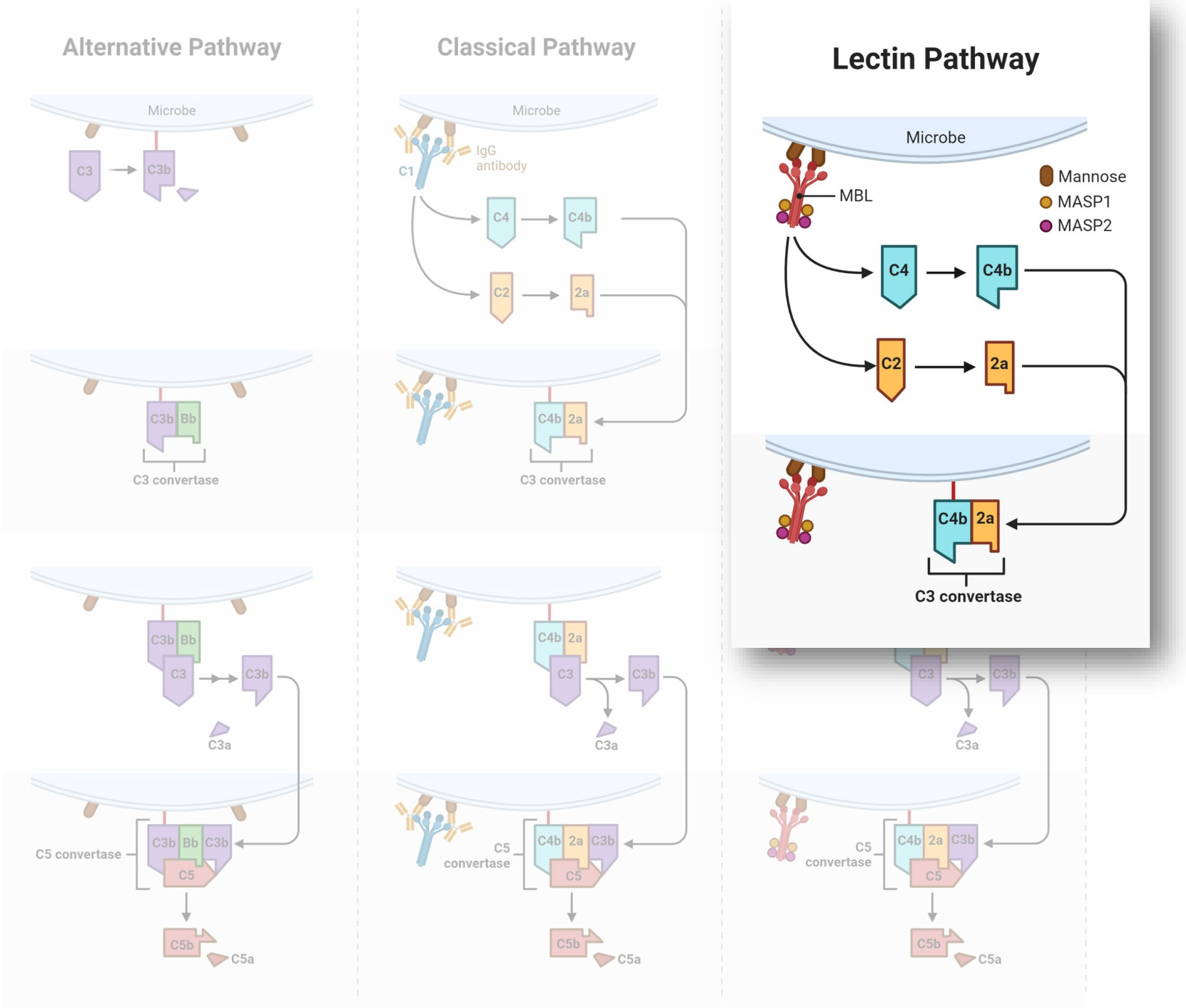

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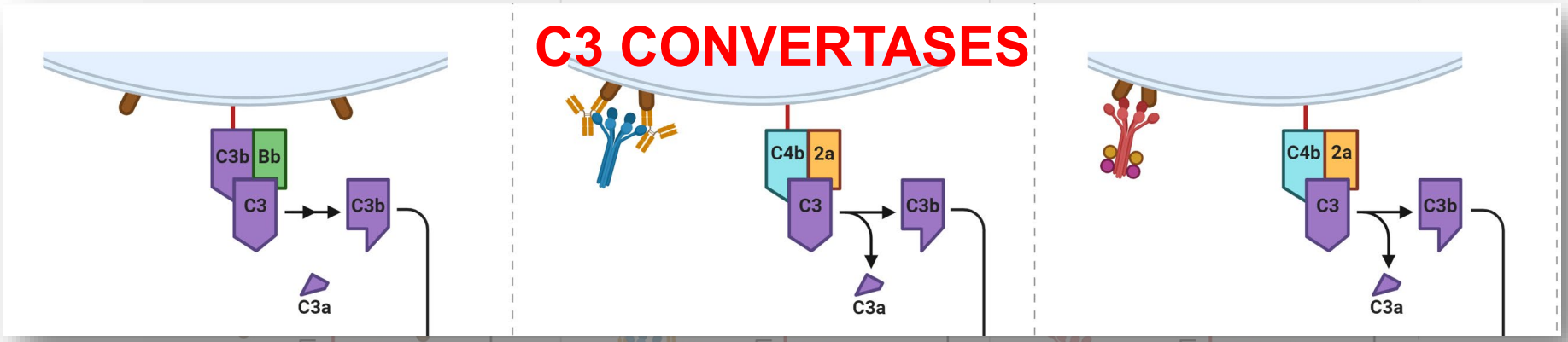

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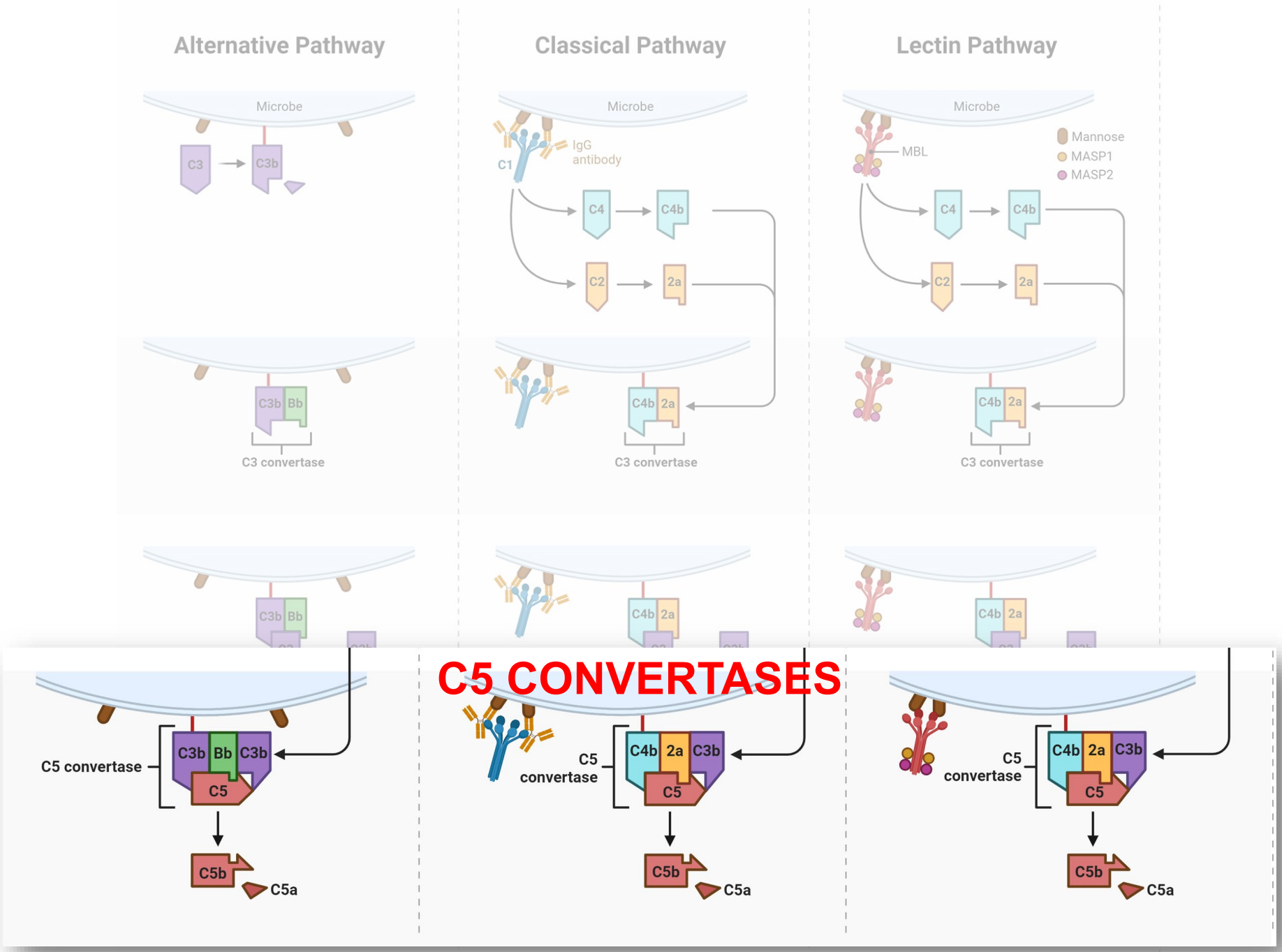

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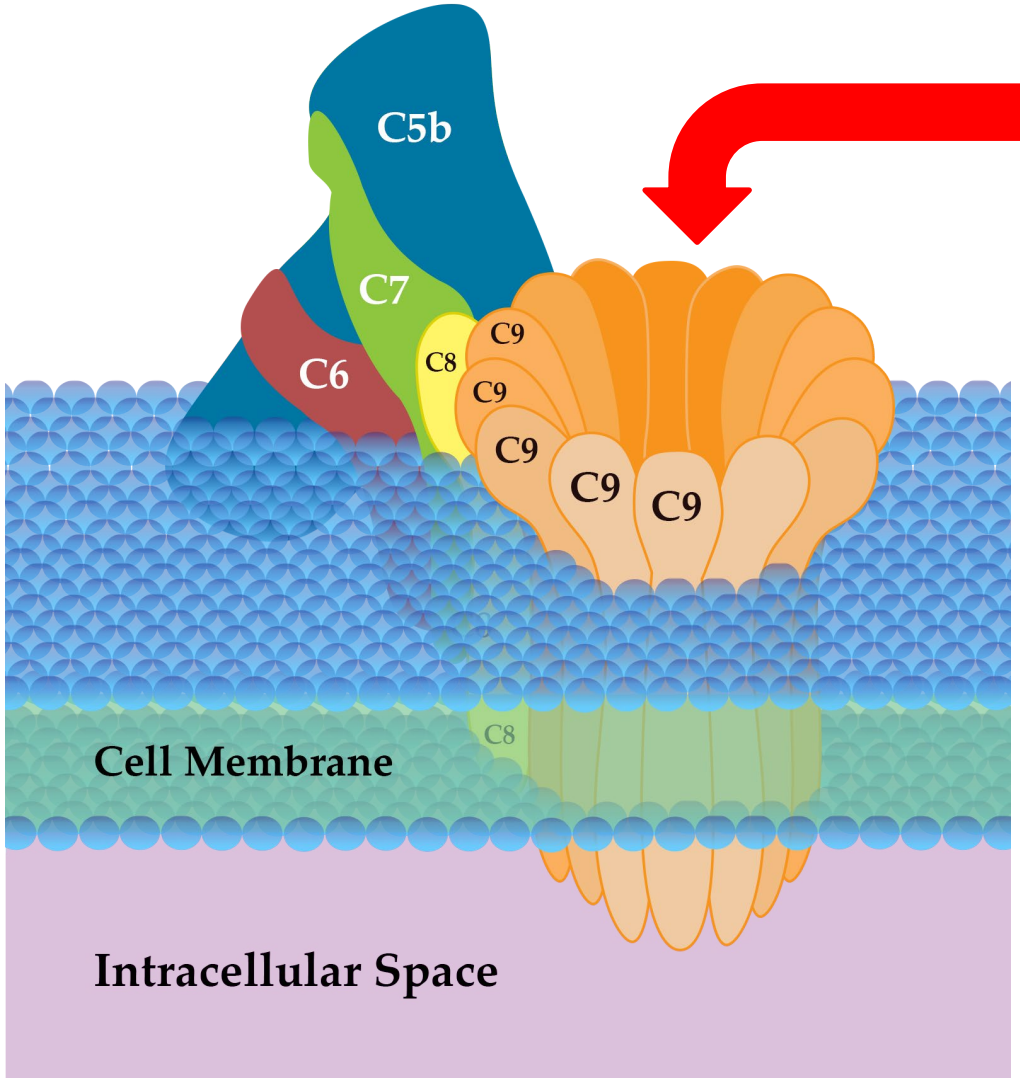
Membrane Attack Complex



Inrushing Fluids

Cell Lysis

https://pressbooks.ccconline.org/bio106/chapter/lymphatic-levels-of-organization/
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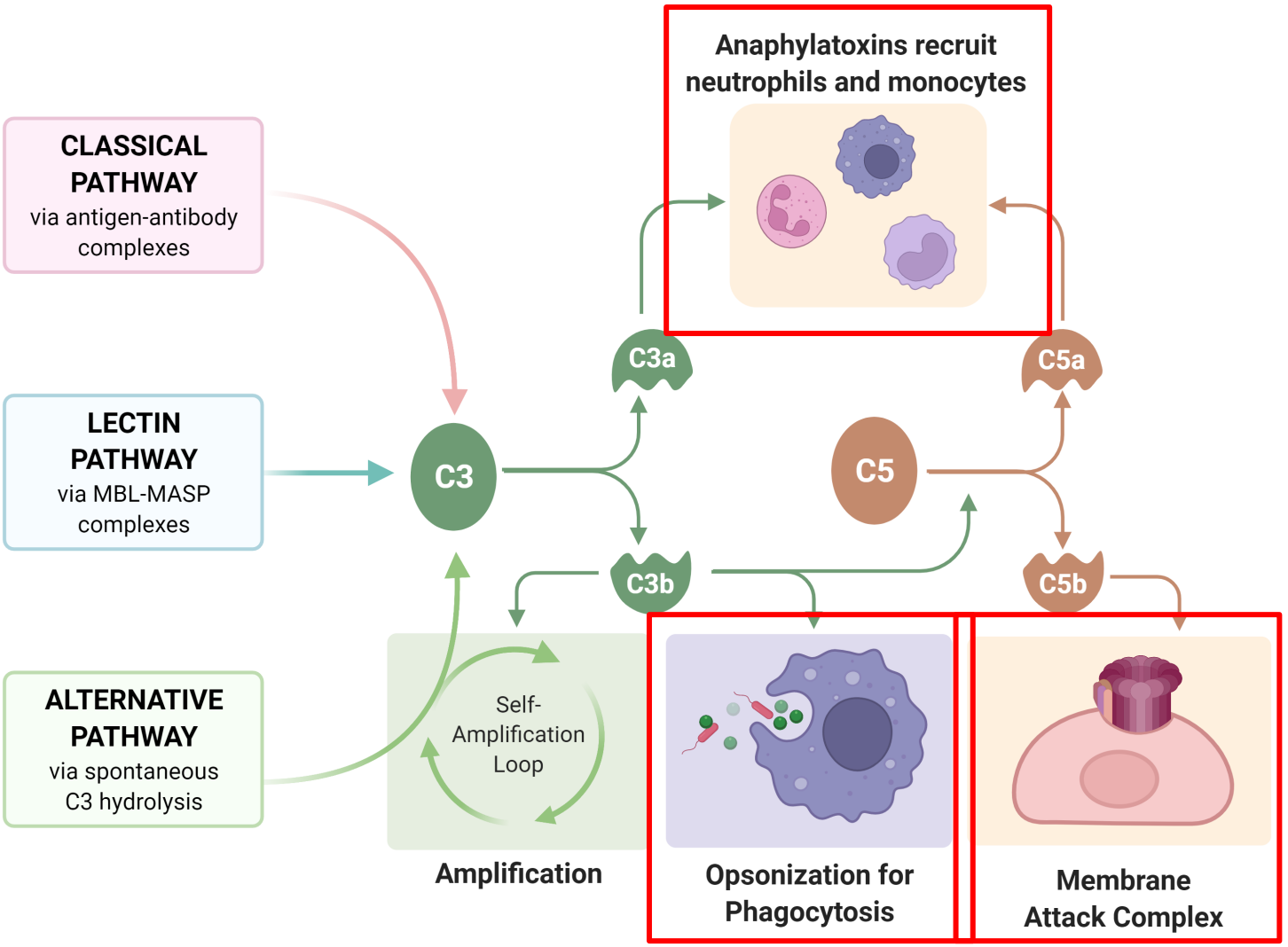
Complement has Several Important Roles in Defense Against Infection



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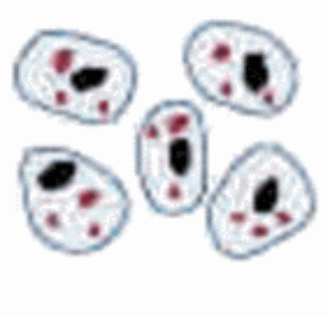
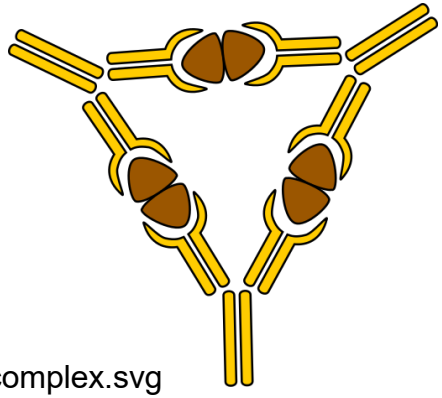
Complement's Other Important Activities

- Interface between innate and adaptive immunity
  - Augmentation of antibody responses
- Disposal of waste
  - Clearance of cellular debris after cell death
  - Clearance of immune complexes





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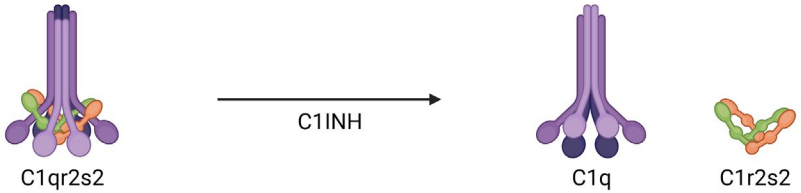
https://vectorportal.com/vector/sweeping/35070
https://commons.wikimedia.org/wiki/File:Structural_changes_of_cells_undergoing_necrosis_or_apoptosis-es.png

Regulation of Complement Activation

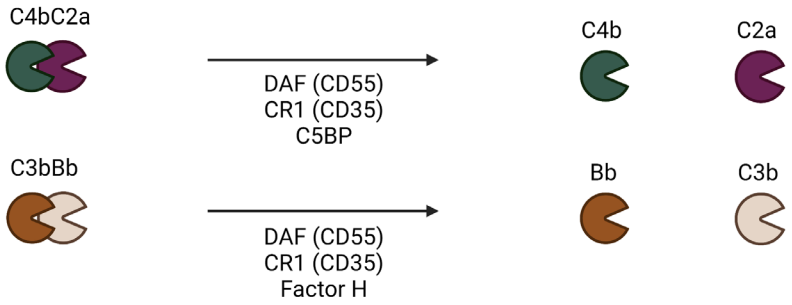
Complement regulation is important to prevent complement-mediated damage to the host

Complement regulation occurs through multiple checkpoints to suppress activation

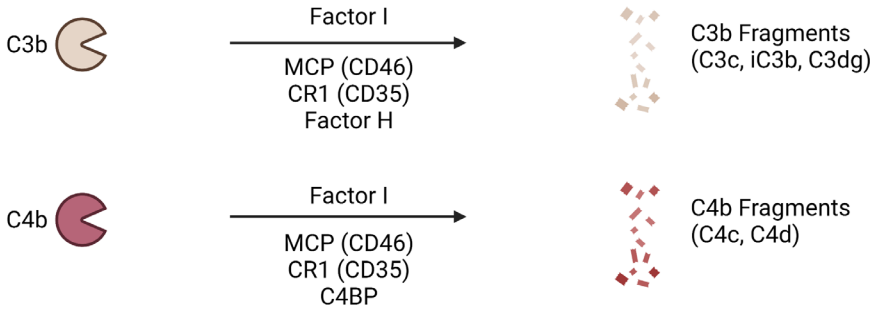
1. C1 Complex Disassembly



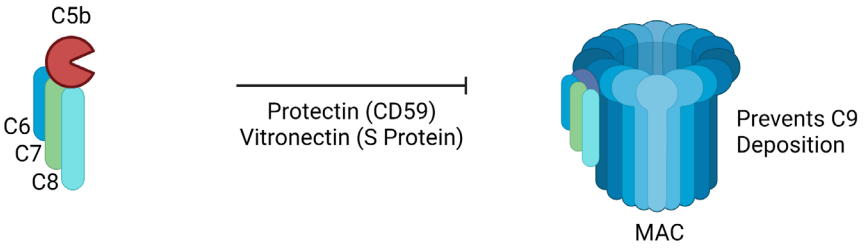
2. C3 Convertase Decay



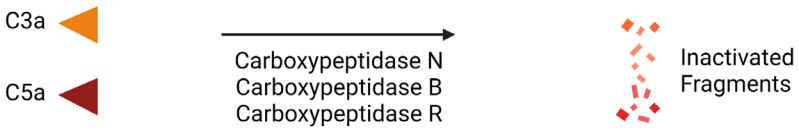
3. Factor I Dependent C3b/C4b Breakdown



4. MAC Inhibition



5. Anaphylatoxin Cleavage



https://commons.wikimedia.org/wiki/File:Complement_Regulation.png

Objectives

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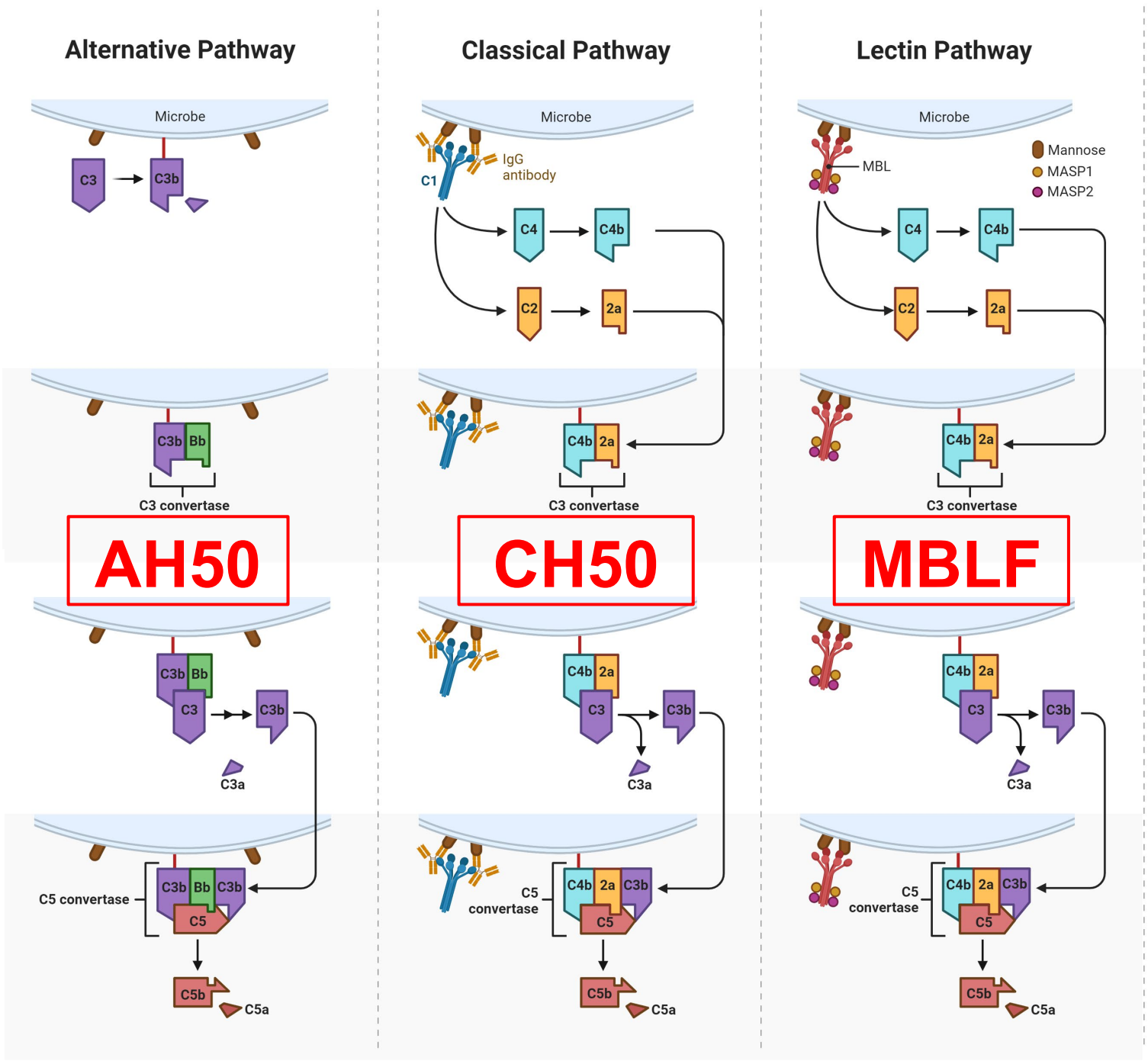
Quantify Complement Components

- Quantifying intact complement factors
  - Measuring C3 and C4 levels are most used in clinical practice and available in many clinical laboratories
- Quantifying other complement factors or activation fragments usually performed by more specialized laboratories
  - Mayo Clinic Laboratories
  - National Jewish Health

Measure Complement Function

- AH50: alternative pathway, functional
- CH50: classical pathway, functional
- MBLF: mannose binding lectin pathway, functional



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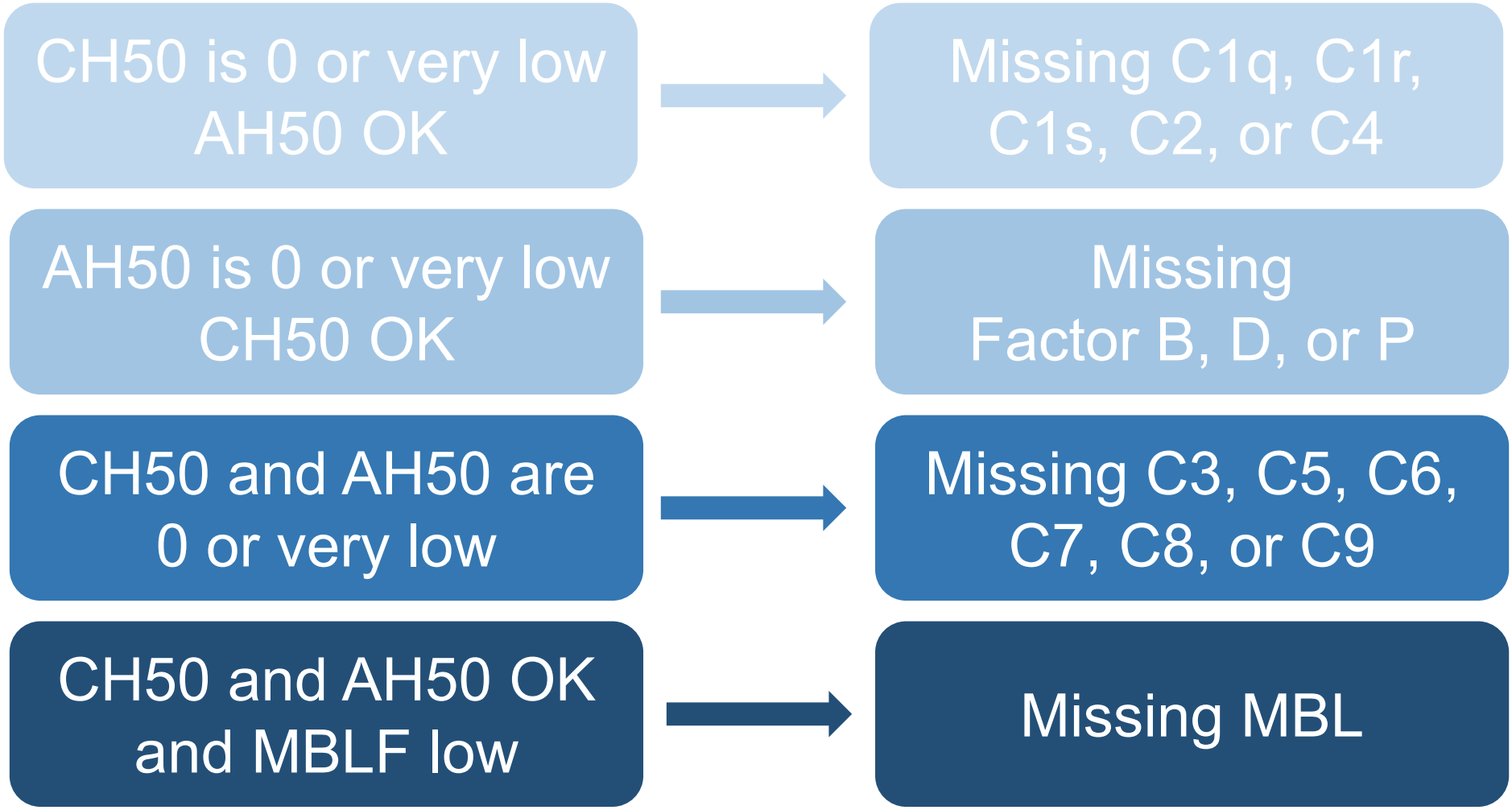
Complement Factor	AH50	CH50	MBLF
C1		✓	
C2		✓	✓
C3	✓	✓	✓
C4		✓	✓
C5	✓	✓	✓
C6	✓	✓	✓
C7	✓	✓	✓
C8	✓	✓	✓
C9	✓	✓	✓
Factor B	✓		
Factor D	✓		
Factor P	✓		
MBL			✓

Lab Results for Complement Deficiencies



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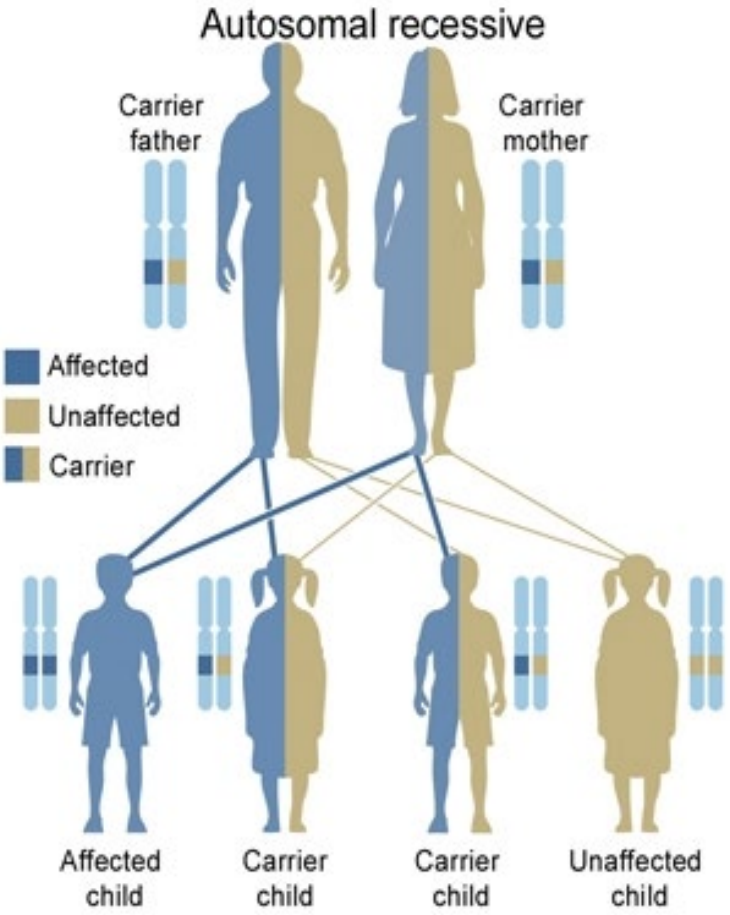
Complement Deficiencies

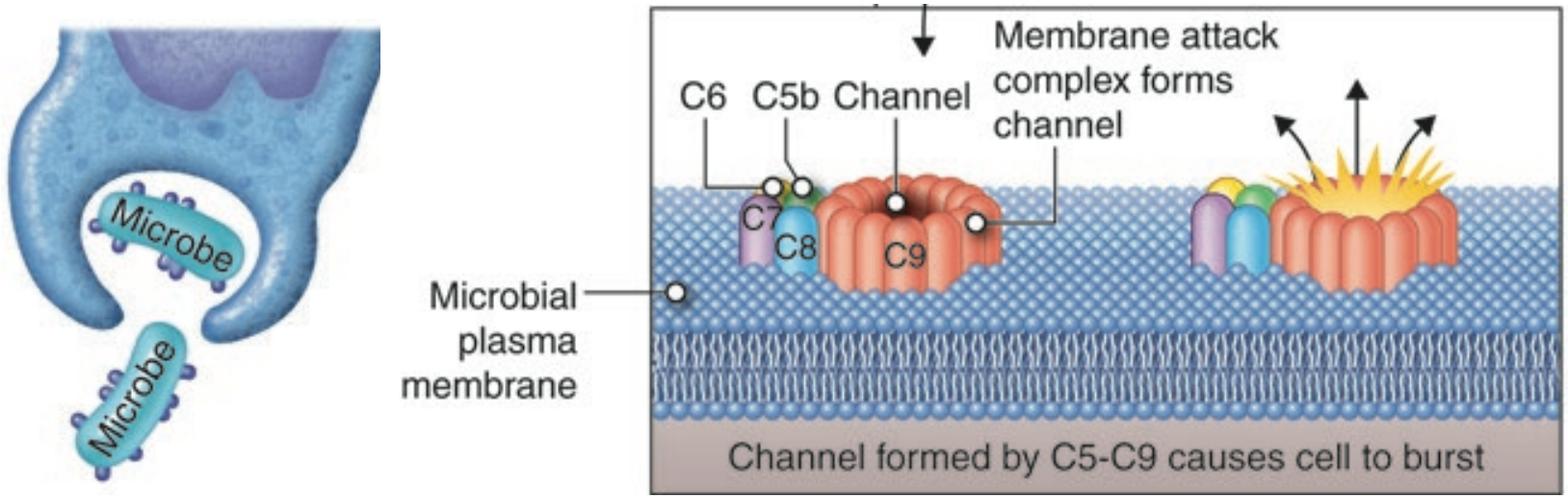
- Represent ~5% of all primary immune deficiencies
- Majority inherited in autosomal recessive fashion
  - C1 inhibitor – autosomal dominant
  - properdin – X-linked
- Most carriers of complement deficiencies are clinically normal or without symptoms



https://commons.wikimedia.org/wiki/File:Autosomal_recessive_inheritance.png

Clinical Features of Complement Deficiencies

- Infections
  - Recurrent sinus and pulmonary infections, particularly with encapsulated bacteria
  - Recurrent infections due to *Neisseria*



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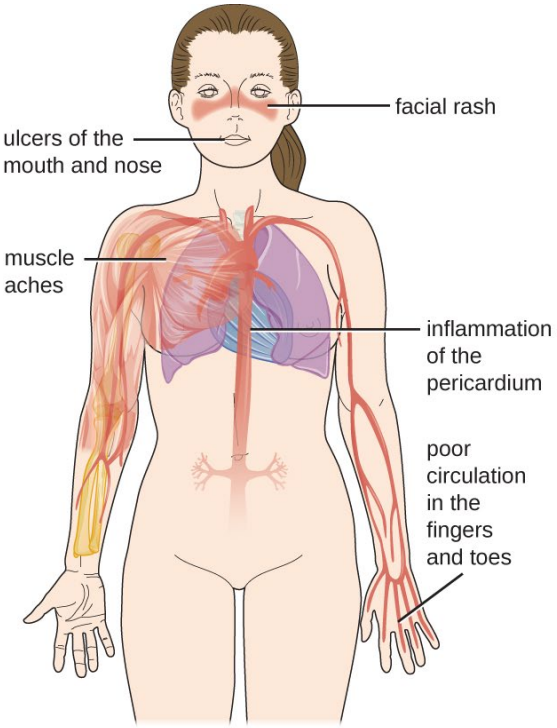
Clinical Features of Complement Deficiencies

- Autoimmunity
  - Systemic lupus erythematosus
  - Kidney disease



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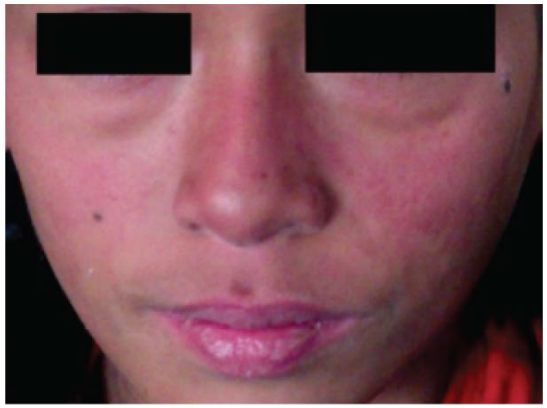

(b)

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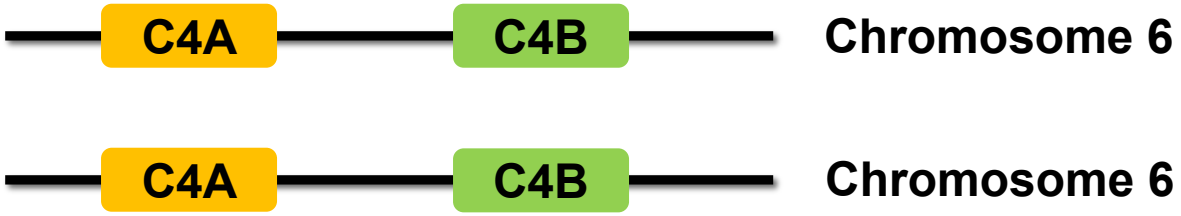
Complement Deficiencies: Recurrent Infections + Lupus

Deficiency	Cases Reported	Clinical Features	Diagnostic Findings



Adapted from: Sullivan KE (2014). The Complement System. In N. Franklin Adkinson Jr [et al, eds] Middleton's Allergy.

Complement Deficiencies: Neisseria Infections

Deficiency	Cases Reported	Clinical Features	Diagnostic Findings

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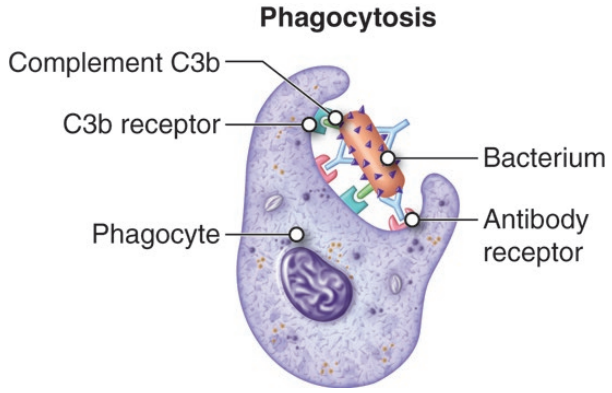
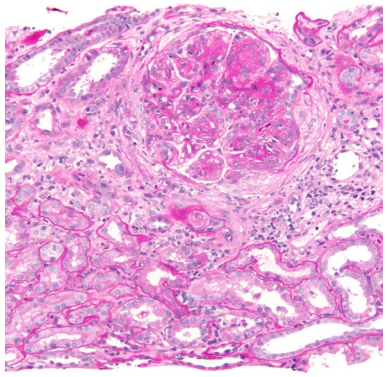
Other Complement Deficiencies

Deficiency	Cases Reported	Clinical Features	Diagnostic Findings

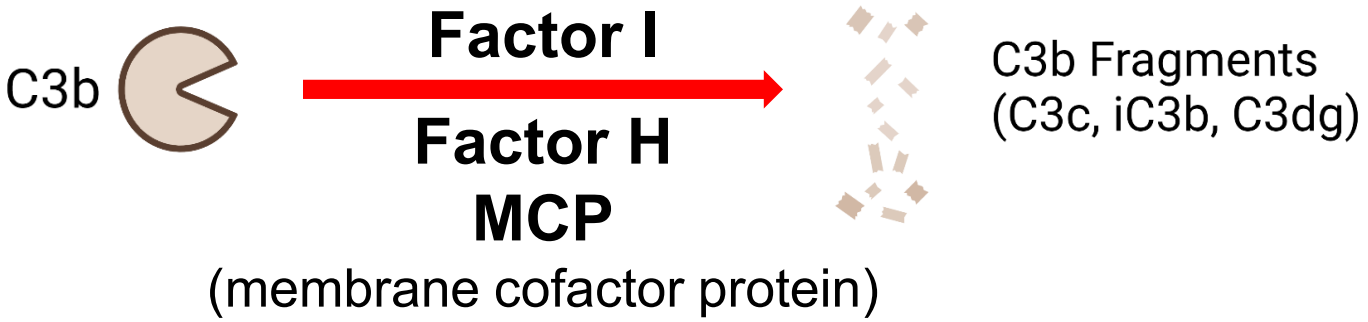




https://pressbooks.ccconline.org/bio106/chapter/lymphatic-levels-of-organization/
https://commons.wikimedia.org/wiki/File:Membranoproliferative_glomerulonephritis_-_high_mag.jpg
Adapted from: Sullivan KE (2014). The Complement System. In N. Franklin Adkinson Jr [et al, eds] Middleton's Allergy.

Deficiencies in Regulators of Complement

Deficiency	Cases Reported	Clinical Features	Diagnostic Findings
Factor I	10-100	*Neisseria* infection Hemolytic uremic syndrome Macular degeneration	C3 may be low
Factor H	10-100	*Neisseria* infection Hemolytic uremic syndrome Macular degeneration	C3 may be low
MCP	<10	Hemolytic uremic syndrome	Genetic testing



https://commons.wikimedia.org/wiki/File:Complement_Regulation.png
Adapted from: Sullivan KE (2014). The Complement System. In N. Franklin Adkinson Jr [et al, eds] Middleton's Allergy.

Deficiencies in Regulators of Complement

Deficiency	Cases Reported	Clinical Features	Diagnostic Findings
C1 inhibitor	Many	Hereditary angioedema	C1 inhibitor levels and function

https://sml.snl.no/angioødem
https://commons.wikimedia.org/wiki/File:Complement_Regulation.png
Adapted from: Sullivan KE (2014). The Complement System. In N. Franklin Adkinson Jr [et al, eds] Middleton's Allergy.

Management of Complement Deficiencies

Take Home Points

- Complement deficiencies are not uncommon
- Recurrent sinus and pulmonary infections, *Neisseria* infections, lupus, angioedema, and kidney disease are the most common clinical presentations
- Diagnosis begins with measuring complement levels and function
- Management is tailored to the deficiency and individual

Thank You!