Complement..

devinson Chapter 63.. #1

The complement system consists of 20 proteins present in the serum. synthesized in the liver.

Three main effects of complement:

1. Lysis of cells. (MAC)
2. generation of mediators. (C_{3a}, C_{5a}... etc)
3. opsonization. (C_{3b})

* Activation of Complement:

Several complement components are proenzymes

↓ must be

cleaved to form active enzymes

can be initated by

- antigen-antibody complexes (1)
- Variety of nonimmunoglob. molecules (2,3)

* Activation of complement components:

occurs via 3 pathways:

- Classic (Acquired)
- Lectin (Innate)
- Alternative (Innate)

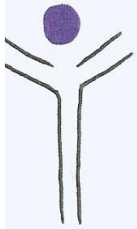
all three: lead to C_{3b} production (central molecule)

has two functions by its presence on the surface of a microbe.

- combines with other complement proteins → generate → C_5 convertase → produce MAC
- opsonizes the Bacteria because phagocytes have C_{3b} receptors

Important for the first time we get infected by that microorganism as the classic pathway needs an antibody.

1 In the Classic Pathway:



Antigen- Antibody complex

+ → C_1 → form → Protease → cleaves → C_2 C_4

C_4b2b

C_3 convertase

cleaves → C_3

C_3 → C_{3a} (Anaphylatoxin) + C_{3b}

C_{3b} → forms complex → C_4b2b3b

C_5 convertase

cleaves → C_5

C_5 → C_{5a} (Anaphylatoxin & chemotactic factor) + C_{5b}

C_{5b} → binds with C_6 C_7 → to form with interaction with $C_8 + C_9$ → C_5b_{6789}

C_5b_{6789} → MAC → Cytolysis

2 In lectin Pathway:

Microbial surface → bind → Mannan-binding lectin → activates → Protease

3) In the **Alternative** pathway:

cell surface substances
(bacteria endotoxin, fungal cell walls, & viral envelops)

↓ binds

$C_3(H_2O)$ + factor B

↓ cleaved by D (protease)

C_{3b}, B_b

C_3 convertase

↓ cleaves

C_3

C_{3a} + C_{3b} + factor H (Binding of)

C_{3b} cleaved by factor I

C_{3b} forms complex

C_{3b}, B_b, C_{3b}

C_5 convertase

This will eventually,
↓ the amount of C_5 convertase
& the C_{3b} can be protected by binding to cell membranes.

↓ finishes the classic pathway.

* **Regulation** of the Complement System: #3

- 1st regulatory step in the classic pathway is at the level of the antibody.
as the complement-binding site on the heavy chain is unavailable to C_1 component if the antigen was absent.
So, if an antigen binds → conformational change → C_1 can bind.

② C_1 inhibitor:
works as a competitive inhibitor to C_1 (no protease activity)

- Regulation of the alternative:
(see image ←)
- Properdin stabilizes C_3 convertase & protects C_{3b}.
- Protection of human cells from MAC, mediated by decay-accelerating factor (glycoprotein)

↓ acts by binding to

C_{3b} & C_{4b}

✗

limits formation of C_3/C_5 convertase

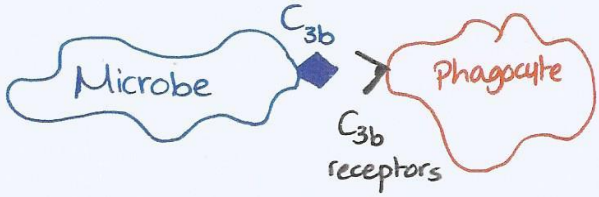
✗

prevents formation of MAC

* Biologic Effects of Complement:-

1 Opsonization:

- Viruses & Bacteria are phagocytized better when they have C_{3b} on its surface, as phagocytes have C_{3b} receptors.



2 Chemotaxis:

C_{5a} ⇒ - Attract neutrophils.
- ↑ adhesiveness of neutrophils to endothelium.

C_{567} ⇒ Attract neutrophils.

3 Anaphylatoxin:

C_{3a}, C_{4a}, C_{5a} (*Most potent*) ⇒ cause degranulation of mast cells ⇒ release of mediators ⇒ ↑ vascular permeability & smooth muscle contraction

Anaphylatoxins can bind to smooth muscle cells of the bronchioles ⇒ Bronchospasm.

4 Cytolysis: by C_5b_{6789}

forms a pore in cells (eg: RBCs, tumor cells, & Bact.) ⟶ allows H_2O & electrolytes to enter → Kills the cells.

5 Enhancement of Ab production:

binding of C_{3b} on its receptors on B cell ⟶ ↑ Ab production

* Clinical Aspects of Complement:

1. Inherited ↓ of some components (C5-C8) ⟶ Bacteriemia (↓MAC) لأن مافي وسيلة دفاع
↓ of Mannan-binding-lectin ⟶ infections.
↓ C_3 ⟶ pyogenis infections & respiratory infections

2. ↓ of C_1 esterase inhibitor ⟶ Angioedema due to
↑ C_1 esterase ⟶ ↑ anaphylatoxins ⟶ ↑ Histamine ⟶
↑ vascular permiability ⟶ edema

3. ↓ "DAF" ⟶ Complement-mediated hemolysis.
because there won't be anything that protects the cells.

4. Transfusion mismatches (Blood type A to Blood type B)
Antigen-Antibody complex activated ⟶ Complement activated ⟶
↑ Anaphylatoxins & MACs ⟶ RBCs hemolysis.

5. Immune complexes ~~attract~~ bind complement ⟶ attracts PMN leukocyte
(Antibody-Antigen)
⟶ release enzymes when degraded ⟶ damage tissues.

6. Severe Liver Disease ⟶ ↑ infections due to ↓ Complement Protein synthesis.