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THE COMPLEMENT SYSTEM

Complement System → comprises of several soluble Proteins.
—— Humoral Immunity ——

→ imp. connection b/w innate & acquired immune response
→ complement system has many imp. functions -
  • act as opsons by binding to antigens & ~~et~~ direct opsonisation.
  • induce inflammation
  • some Proteins can induce direct lysis of pathogens
→ Heat-sensitive
→ complements the function of antibodies; however it can work independently by recognising PAMPs.
  Ab-dependent / Ab-independent
→ soluble proteins; some can be cell-bound
→ mainly produced in the liver
→ They are present as pro-enzymes (zymogens) and they get activated upon proteolytic cleavage. inactive

FUNCTIONS:
(i) Lysis - Bacterial & viral infected cells are targetted
  - lysis through Membrane Attack Complex (MAC)
(ii) ~~opso~~ opsonization
(iii) Inflammation
(iv) Immune clearance - removes immune complexes from circulation

Complement Activation:
(i) Classical Pathway
(ii) Alternative Pathway
(iii) Lectin Pathway
The starting points are diff., however all 3 Pathways will converge when C3-convertase enzyme is formed.

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— Classical Pathway
- Ab-dependent
- Begins with Ag-Ab complex formation
- Acquired immune response

— Alternative Pathway
- Ab-independent
- Initiated by PAMP recognition
- Innate immune response

— Lectin Pathway
- Ab-independent
- Activated when mannose-binding lectins recognise mannose residues on the pathogens
- Innate immune response

Nomenclature:

Complement Proteins can be designated by numbers or letters.

eg:
- C1 — C9
- Factor D, Factor B, Factor H

Comp. Proteins are often activated by Proteolytic cleavage.

Fragments formed ⇒ a, b
(a: smaller fragment; b: bigger fragment)

eg: C3a (small), C3b (big)

Exception → C2 : C2a (big), C2b (small)

Proteolytic activity of other complement proteins

In the Pathway, these Proteins can associate with other Proteins to form an enzyme complex (enzymatically-active), they are represented by a bar on top.

eg: $\overline{C4b2a}$

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Classical Pathway :-

→ Ab-Ag binding

only IgM, IgG1, IgG2, IgG3 (human) ~~complex~~ binding can initiate ↓ ~~this~~ this ↓ pathway.

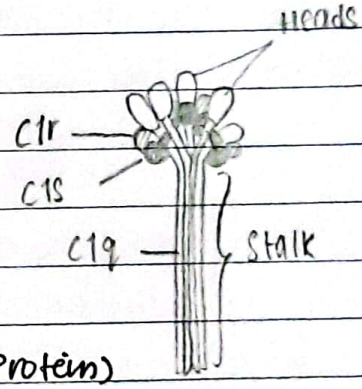
10 epitopes binding — 2 epitopes binding

IgM efficiency is high!

→ When Ag binds to Ab, it ~~co~~ causes a conformational change in the Fc site of Ab.
This change exposes a binding site for C1 complement molecule.

C1 molecule:

- $C1q r_2 s_2$ → 2 r subunits (C1r)
  ↳ 1 q subunit (C1q) → 2 s subunits (C1s)
- complex is stabilized by Ca^{2+} ions
- r, s subunits → ~~Proteases~~ Proteolytic activity
  q subunit → ~~binds to Ag~~ antigen complement protein) (activates other



C1 molecule

- When r, s subunits are activated, it can proteolytically cleave C4, C2 complement proteins.
- C4 → C4q - released out of the cell; inflammation activity
  ↘ C4b - binds to ~~bacte~~ pathogen surface
- C2 → C2q - binds to pathogen surface
  ↘ C2b - released out of the cell; inflammatory function

- C4b, C2q complexes form C3-convertase complex.
  C3-convertase cleaves C3. C3 convertase – $\overline{C4b2a}$

- C3 → C3q - released out
  ↘ C3b - binds to pathogen

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- C4b, C2a, C3b complexes forms C5-convertase complex.

The C3b part of C5-convertase binds C5, allowing C5 convertase — $\overline{C4b2a3b}$
$\overline{C4b2a}$ to cleave C5.

- C5 → C5a — released out
  ↘ C5b — binds to Pathogen.

- C4b, C2a, C3b, C5b complex recruits other ~~ED~~ Proteins: C6, C7, C8 & C9.
  (C6, C7, C8 & C9: do not have proteolytic cleavage)
- These Proteins recruits more of their types and assemble to form the Membrane-attak complex.

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~~NOTE:~~ ~~Liver transplants are more successful due to the fact that the hepatic cells don't express MHCs much.~~

Membrane attack complex-

- C5b attaches to C6, then to C7 and the C5b67 complex inserts into the membrane
- C5b67 complex binds with C8 to induce a 10 Å pore on the membrane.
- This induces C9 to bind with C5b678 complex and Polymerisation of C9 around C5b678 results in the formation of a Perforin-like molecule, thus increasing the ~~is~~ Pore size.
- The completed Membrane-attack complex (MAC) has a tubular form and functional Pore size of 70-100 Å.

NOTE: All the steps in the 3 Pathways after formation of C3 Convertase remains the same for all 3 complement Pathways.

- The structure of the MAC disintegrates the membrane of the Pathogen ~~and~~, thus, killing it.

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Lectin Pathway :-

→ Lectin : Proteins that bind to a carbohydrate

→ MBL (Mannose-binding lectin) -

It is an acute phase response protein released by the liver during an infection, that binds to mannose residues on the surface of pathogens.

NOTE: MBL does not bind to host carbohydrate residues because it is protected by Sialic acid residues.

→ MASP-1 & MASP-2 (MBL-associated serine protease) -

It has proteolytic activity. It cleaves C4 and C2 molecules.

→ MBL : similar in structure to C1q

MASP-1, MASP-2 : similar in structure to C1r and C1s respectively.

- MBL binds to mannose residues and recruits MASP-1 and MASP-2.
- MASP-1 & MASP-2 cleaves to C4 and C2.
- Rest of the pathway is similar to Classical Pathway.

→ Since the Lectin Pathway is Ab-independent, it is activated during Innate immune response (initial inflammatory response).

NOTE: Lectin Pathway is an imp. innate defense mechanism comparable to Alternative Pathway but utilizing elements of the Classical Pathway.

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Alternative Pathway :-

→ Like Lectin Pathway, Alternative Pathway also doesn't require Ab for activation, therefore, it is a component of the innate immune system.

→ It is initiated by cell-surface constituents that's foreign to the host. ↳ can be activated by host proteins as well

eg: Bacterial cell wall, PAMPs.

→ Exceptions : • C1, C4, C2 are not involved in alternative pathway
• C3 convertase is made of diff. comp. prot. (C3, factor B, factor D, Properdin).] serum proteins

- C3 can undergo hydrolysis by itself, due to its unstable thioester bond, and form C3a and C3b.
- C3b will associate with factor B.
- This complex will recruit factor D that will cleave factor B to larger and smaller fragments.
- Larger fragment associates with C3b, forming C3 convertase (but, unstable) ↳ C3 convertase — $\overline{C3bBb}$ analogous to C42ba complex in the classical pathway
- Properdin induces stability of C3 convertase.
- The rest is similar to other two pathways.

NOTE : Cells can control levels of properdin which allows the control of C3 convertase levels in the cell.

Where do the Pathways converge?

The three complement pathways converge at the production of an active C3 convertase.

POINTS TO NOTE: * C3b can act as opsins & induce Phagocytosis
* C3b can bind to Ag-Ab complex & promote Phagocytosis
* C3a, C5a are other inflammatory factor.

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Regulation of Complement System:

Regulation helps distinguish b/w Pathogens & self cells.

Types:

(i) Passive regulation
Highly & unstable components (enzyme complexes) are ~~regulated~~ stabilized by the levels of other components which is controlled by the cells.

~~eg~~

(ii) Active regulation
When there are regulatory proteins that regulate the complement system.

eg: C1 inhibitor → Serine Protease inhibitor: causes $C1r_2s_2$ to dissociate from C1q
[Classical Pathway]

eg: C4b-binding Protein (C4bBP) → Blocks formation of C3 convertase by binding to C4b
[Classical, Lectin Pathway]

eg: Factor H → Blocks formation of C3 convertase by binding to C3b
[Alternative Pathway]

eg: Complement receptor type 1 (CR1/CD35), Membrane co-factor protein (MCP/CD46) → Block formation of C3 convertase by binding C4b or C3b
[Classical, Lectin, Alternative Pathway]

eg: Decay-accelerating factor (DAF/CD55) → Accelerates dissociation of C4b2 and C3bBb
[Classical, Lectin, Alternative Pathway]

eg: Factor I → Serine Protease: cleaves C4b or C3b using C4bBP, CR1, factor H, DAF, MCP as cofactor.
[Classical, Lectin, Alternative Pathway]

eg: S Protein → Binds soluble C5b67 & prevents its insertion into cell membrane (prevents membrane Attack complex)
[Terminal]

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eg: HRF (Homologous restriction factor) → Prevents assembly of MAC; known as membrane inhibitor of reactive lysis (MIRL or CD59)
[Terminal]

eg: Anaphylatoxin inactivator → Prevents proteins associated with inflammatory response
[Effector]

Other functions of the complement system:

* Act as opsons.

eg C3b is an imp. complement protein that act as an opsonin by binding to Ab-Antigen complex.

* Cell lysis
* Viral neutralisation

→ Forms aggregates with viruses upon recognition & aids in phagocytosis of these aggregates.

* Solubilization & clearance of immum complexes.

→ Part of Adaptive immune response.

eg C3b binds to antigen-antibody complexes & take them to the spleen & liver to present them to phagocytes.
↳ example of opsonization

* Inflammatory response

eg: C3a, C4a, C5a → Anaphylatoxin activity
Induce degranulation with release of Histamine
imp. inflammatory Protein

Complement-binding receptors:
Receptor — Ligand (Complement Proteins).

The cells that recognise these receptors include cells of both the Adaptive & innate immunity.

eg: The C3b protein recognizes the CR1 receptor present on Erythrocytes. Upon binding, it travels through the blood stream (via the RBCs) to the spleen or liver.