THE IMMUNE SYSTEM

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Note on References

See box to the right for reference notations.

PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.

Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

What is the Immune System?

- **The immune system is a complex network of cells and proteins designed to neutralize pathogens (including tumour cells) and clear out damaged cells.**

How crucial is each element of the immune system?

Examples

- **The HIV virus attacks a primary component of the system: the T-helper (CD4+ cell) (1pm, 2pm, 3pm). Macrophages and dendritic cells may also be affected, but it is the decline of CD4+ T-cells that incapacitates cell-mediated immunity and allows opportunistic infections to gain a foothold, leading to devastating effects.**
- **Many congenital immunodeficiencies are due to the lack of a single component: for examples X-linked and recessive agammaglobulinaemia (B-cell deficiency); selective IgA deficiency, and other primary immune deficiencies. These deficiencies lead to serious clinical diseases.**

What are the divisions of the immune system?

The divisions (1pm, 2pm, 3pm) are:

- **Innate immune system**
- **Adaptive immune system**
- **Humoural immune system**

What is the Innate Immune System?

The innate, or *non-specific*, immune system consists of the the first responders to any threat.

It includes leukocytes (macrophages, neutrophils, basophils, eosinophils, dendritic cells), mast cells, natural killer cells, and the complement cascade.

All of these are activated directly in the presence of any threat.

The innate immune system is chiefly responsible for the phenomenon of inflammation (1pm, 2pm) .

What are the major features of the innate immune system?

- Movement of immune cells to sites of infection.
- Activation of the complement cascade to attack and neutralize injurious agents.
- Identification and removal of foreign substances by specialized white blood cells.
- Activation of the adaptive immune system through antigen presentation.
- Act as a physical and chemical barrier to infectious agents.

What is the adaptive immune system?

- **The adaptive immune system, a.k.a. *specific* or *acquired* immune system, is the portion of the system which learns to recognize specific pathogens and provides long-lasting immunity against them.**
- **The process of vaccination specifically utilizes the adaptive immune system to protect against specific common pathogens.**

What are antigens?

- Antigens (1w) are foreign substances that can induce an immune response. More specifically, antigens are substances which can bind to antibodies or to T-cell antigen-receptors. Antigen binding to T-cells causes different forms of activation according to the receptor bound.
- Antigens are usually amino acid complexes (proteins, polypeptides, peptide chains) or polysaccharides. Lipids and nucleic acids must combine with amino acid complexes to become antigens.
- Immunogens (1w) are antigens which can trigger an immune response.

What is a major histocompatibility complex (MHC)?

- A major histocompatibility complex (MHC) is "a set of genes that code for cell surface proteins that are essential for the acquired immune system to recognize foreign molecules".
- Cell-surface MHC molecules bind to antigens derived from pathogens and display them on the cell surface for recognition by the appropriate T-cells (antigen presentation)
- Human Leukocyte Antigen complex (HLA alleles) (1ow, 2i) are gene complexes which encode the MHC proteins. Certain HLA alleles are linked with autoimmune diseases: HLA-B27, for instance, is associated with inflammatory autoimmune conditions such as ankylosing spondylitis.

What are major histocompatibility complex (MHC) molecules?

Major histocompatibility complex (MHC) molecules (1w, 2i) are specific proteins also known as Human Leukocyte Antigen complex (HLA), presented on the cell surface.

- Class I MHC (1w, 2i, 3rg)– found in all nucleated cell; they bind to peptides produced within the cell, such as viral antigens. Target virus-infected cells for cytotoxic (CD8+) T-cells (1w, 2i).
- Class II MHC (1W, 2i, 3rg) – found only on antigen-presenting cells. Bind to extracellular peptides, suc,h as bacterial proteins. Essential for stimulating helper (CD4+) T-cells (1i, 2w).

What are antigen-presenting cells (APCs)?

- Antigen-presenting cells (1i)are those cells that intake antigens, process them internally, and present peptide fragments to T-cells.
- Professional APCs (1w, 2i) specialize in presenting antigen to T cells. Those that display MHC II molecules interact with CD4+ ("helper") T-cells; those that display MHC I molecules interact with CD8+ ("killer" or cytotoxic) T-cells.
- The professional APCs are:

  Dendritic cells

  B-cells

  Macrophages

What are the cellular components of the innate immune system?

- Mast cells
- Macrophages
- Neutrophils
- Dendritic cells
- Basophils
- Eosinophils
- Natural killer cells
- Gamma/delta T cells

What are the cellular components of the adaptive immune system?

- T-cells
- B-cells
- Dendritic cells

Where do T-cells originate and mature?

- Lymphoid precursor cells are generated in the bone marrow and move to the thymus, where they undergo positive and negative selection and mature.
- The “T” in T-cell identifies its maturation in the thymus.

What is positive selection?

Positive selection (1yt, 2i) is the process of selecting for T-cells which can engage with MHC molecules.

- Initially maturing T-cells in the thymus become double-positive (CD4+/CD8+) thymocytes.
- Epithelial cells in the thymic cortex express MHC type I and II.
- T-cells which interact appropriately with MHC I downregulate CD4 protein to become CD8+ (cytotoxic T-cells).
- T-cells which interact with MHC II downregulate CD8 to become CD4+ (helper T-cells).

What is negative selection?

Negative selection is the removal or alteration of cells which respond excessively to self-antigens.

- **Thymocytes that have undergone positive selection migrate to the medulla of the thymus.**
- **They are presented with MHC II self-antigens.**
- **If the thymocyte responds too strongly to self-antigens, it either receives an a signal for apoptosis, or becomes a regulatory T-cell (T_{REG}).**
- **Negative selection may be a means of safeguarding against autoimmunity (1pm).**

Where do B-cells originate and mature?

- B-cells originate and mature in the bone marrow (B for Bone).
- Like T-cells, they undergo positive selection (based on the effectiveness of the B-cell receptor, or BCR, on the cell's membrane).
- They also undergo negative selection:

- B-cells that bind too strongly to self-antigens may be deleted, undergo receptor editing, have anergy (lack of immune response) induced, or continue to develop in "ignorance" (ignoring the signals for apoptosis or anergy)

- Immature B-cells migrate to the spleen to complete maturation and become naïve B-cells: that is, they have not been exposed to a pathogen which determines the nature of the antibodies they will produce.

How do B- and T-cells differentiate?

- Naïve B- and T-cells – present in plasma, but not activated by presence of an antigen. Can become either:
- Effector Cells– have been activated by a cognate antigen (antigen which can interact with the membrane receptors), actively involved in pathogen elimination.
- Memory Cells – survivors of pathogen exposure; prepared to mount a swifter and more robust response when the same pathogen is recognized again (immunization).

What are the types of effector T-cells?

Effector T-cells are:

CD4+/ "helper" T-cells. Subtypes:

- **T_H1 cells (1ow, 2w, 3i) – produce interferon-γ; stimulate antibody production in B-cells.**
- **T_H2 cells (1w,)) produce the cytokines (small cell-signaling proteins interleukin-4 [stimulates B-cell immunoglobulin isotype switching] and interleukin-5 [increased eosinophil induction]).**

CD8+/ "killer" T-cells (cytoxic T-cells) (1w, 2i).

- Directly cytotoxic; destroy infected/damaged cells by means of perforin (a cytolytic protein which opens holes in membrane) and granzyme (a protein that induces apoptosis).

What other types of T-cells are there?

- Regulatory T-cells (T_{reg}) (1pm, 2i) and their derivative follicular regulatory T-cells (TFR) (1i) – suppress inappropriate autoimmune responses (negative regulation).
- Follicular helper T-cells (T_{fh}) (1w, 2i) are a CD4+ population which migrate to follicular B-cells and stimulate them to produce high-affinity antigens.
  - Excessive amounts of T_{fh} cells can lead to severe auto- immune disorders; they have been implicated in systemic lupus erythematosus and rheumatoid arthritis, among other diseases also characterized by a decrease in TFR cells.

What is co-stimulation?

- Co-stimulation(1pm, 2pm, 3pm, 4pm, 5pm, 6w, 7i) is the process by which a T-cell or B-cell, through interaction with another immune system cell, becomes fully activated and able to proliferate.

How does co-stimulation work in T-cells?

- 1) The T-cell receptor interacts with the MHC II/peptide molecule presented by an antigen-presenting cell (antigen-specific signal).
- 2) The CD28 T-cell protein interacts with CD80 (B7-1) and CD86 (B7-2) on the membrane of an antigen-presenting cell, producing a non-antigen-specific signal (1pm) which promotes T-cell proliferation and differentiation, and is needed for long-term survival.

How does co-stimulation work in B-cells?

1) The B-cell receptor (BCR) binds an antigen; the antigen is processed and presented on the B-cell's MHC II molecule.

2) An antigen-specific T_H2 cell binds to the MHC II/antigen complex.

3) The T_H2 cell synthesizes and presents CD40 ligand (CD40L or CD154), which binds to the B-cell CD40 protein in order to co-stimulate B-cell proliferation. B-cells cannot proliferate without co-stimulation (see images for details).

4) B-cells can also be co-stimulated by a fragment of the C3b complement component (see selected images).

What are dendritic cells?

- Dendritic cells (1w, 2i) are professional antigen-presenting cells (APCs): they specialize in presenting antigens to T-cells.
- They are a major messenger between the innate and the adaptive immune system.

Where are dendritic cells found?

- Immature dendritic cells are found in epithelial tissue.
- Contact with antigens activates dendritic cells.
- Activated dendritic cells (1w) migrate to lymph nodes and present peptide fragments (the antigens) to activate T- and B-cells.

What is the humoural immune system?

- The humoural immune system (1w, 2i, 3ow) is that part of the immune system comprised of molecules in extracellular fluid (the body's "humours").
- It includes immunoglobulins (1w) (secreted by B-cells), the complement cascade, and anti-microbial peptides.

What do immunoglobulins do?

Immunoglobulins (1w, 2i) do the following:

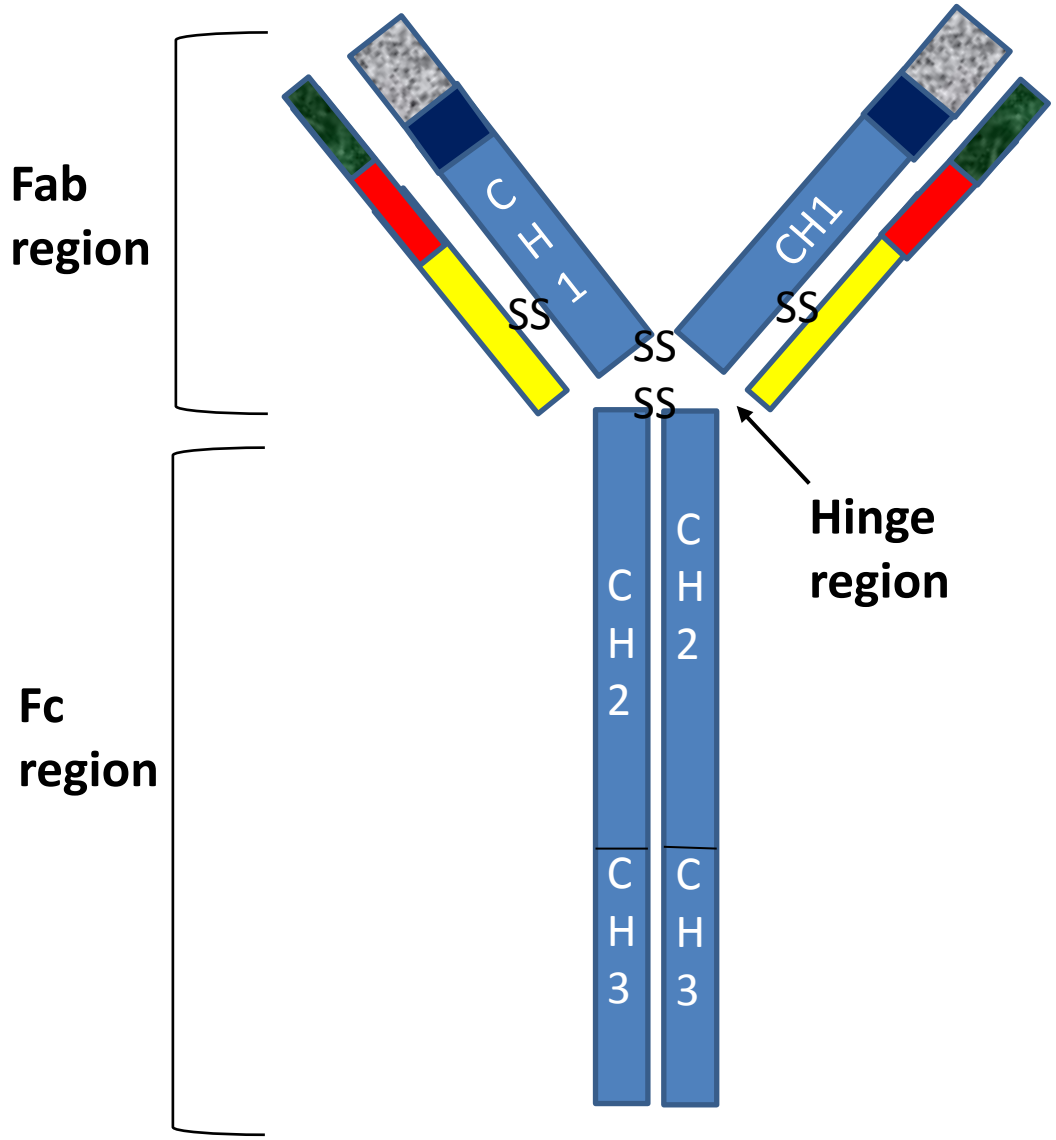
1. **Neutralize pathogens**
2. **Agglutinate foreign cells (for phagocytosis)**
3. **Precipitate serum-soluble antigens (for phagocytosis)**
4. **Activate the *complement cascade* (described in detail below).**

What is the basic structure of an immunoglobulin?

The Basic Structure of Immunoglobulins (1pm)

- **2 heavy chains and 2 light chains form a Y-shaped structure.**
- **The upper tips of the Y are the sites that bind to specific antigens. This is also called the *hypervariable region*, because it differs for each antigen.**
- **The top of the Y is called the Fab, or fixed antigen-binding region.**
- **The stem of the Y is called the Fc, or fixed crystallizable region.**
- **Both heavy chains and light chains have constant, variable, and hypervariable regions.**

Basic Immunoglobulin Structure



Hypervariable region – heavy chain

Variable region – heavy chain

Constant region – heavy chain

Hypervariable region – light chain

Variable region – light chain

Constant region – light chain

Fab – Fragment, antigen-binding
Fc – Fragment, crystallizable
SS – disulfide bond

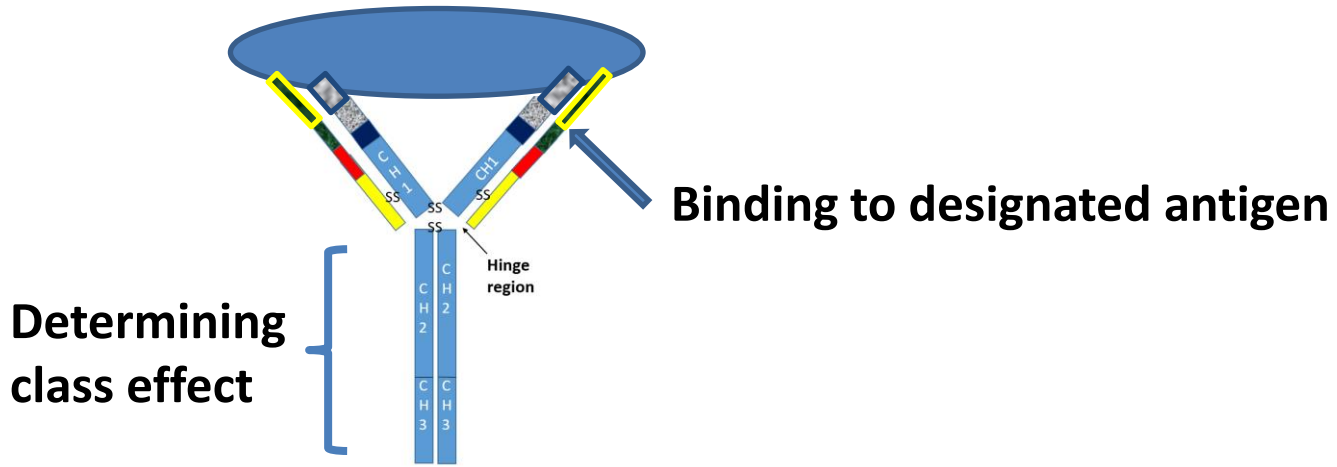
Fab regions are the site of antigen binding.

Who elucidated the chemical structure of immunoglobulins?

- Gerald Edelman, for which he received the Nobel Prize in 1972.

How do immunoglobulins function?

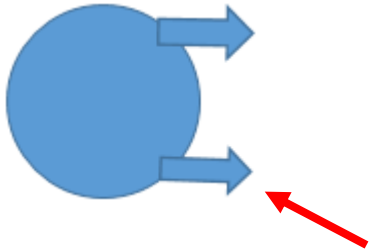
- **The hypervariable region at each tip of the Y binds to its designated antigen on a pathogen or infected cell surface membrane.**



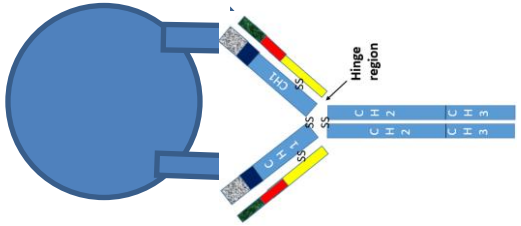
- **The Fc region determines the *class effect* (the different isotypes of immunoglobulins).**

Antibody effects on pathogens

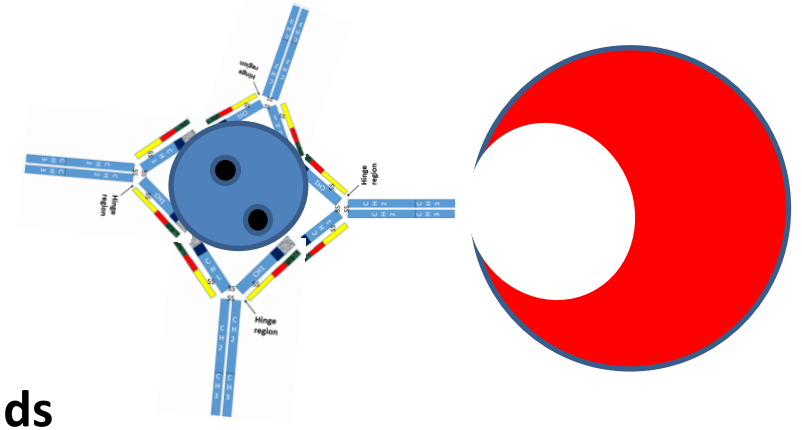
- **Antibody binding can also block receptors crucial to pathogen function and infectivity.**



Receptors involved in host cell entry



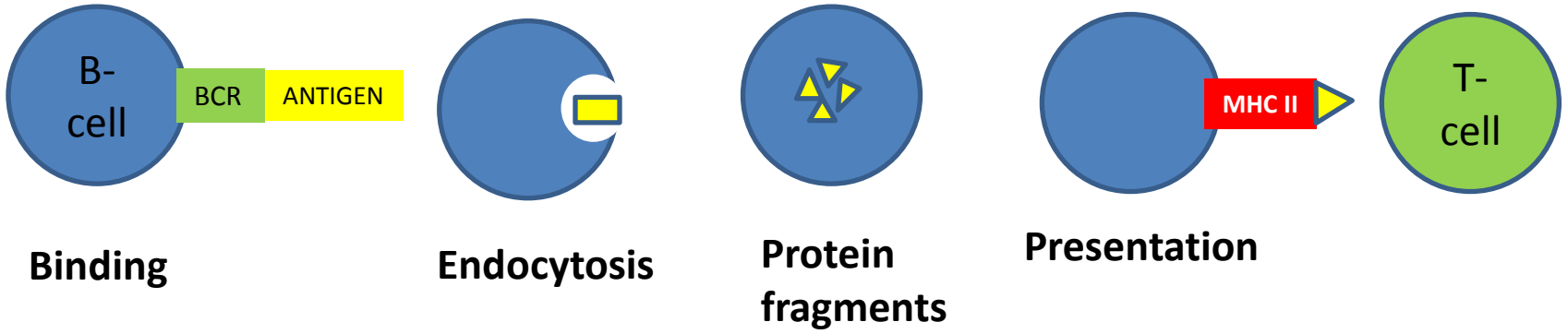
Hypervariable region binds and blocks pathogen entry receptors



Antibody binding also marks the pathogen for phagocytosis and activates the complement system to breach the pathogen's membrane.

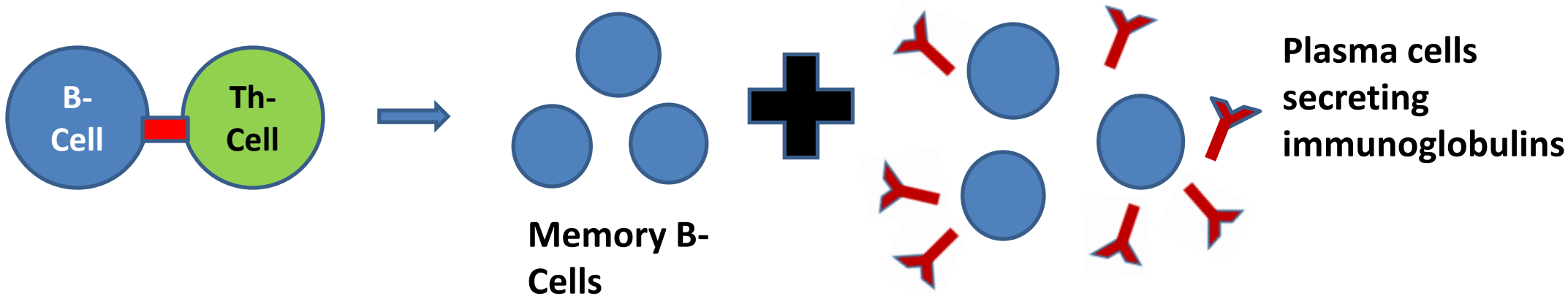
How are immunoglobulins produced?

- The B-cell receptor (BCR)(1pm) on a B-cell's membrane binds to an antigen.
- The antigen is taken in by endocytosis, processed, and presented on an MHC II molecule on the B-cell's membrane to T cells to trigger their immune responses.



Activation and proliferation

- A T_H cell binds and is activated, producing cytokines that lead to clonal proliferation of the B-cell.
- Some of the clones become memory B cells; others become plasma B cells, which secrete large numbers of immunoglobulins targeted towards the specific antigen (via hypervariable regions).



What are the classes of immunoglobulin?

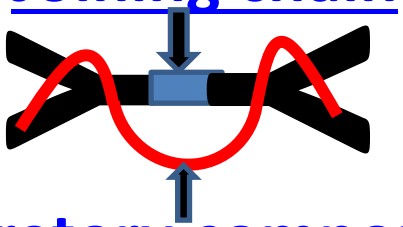
- IgA
- IgD
- IgE
- IgG
- IgM

The *constant region* of the heavy chains (1w) differs for each class of immunoglobulin, so that they are able to bind to different effector molecules.

The *variable region* remains the same, so that different classes of immunoglobulin can target the same antigen.

What does Immunoglobulin A (IgA) do?

- Immunoglobulin A (IgA) (1i) is an antibody that mediates the immune function of mucous membranes.
- IgA is secreted by mucosa and in breast milk.
- It provides an early defense against orally ingested or inhaled pathogens.
- Symptoms of IgA deficiency are repeated or chronic respiratory tract infections (both upper and lower) and diarrhea.
- Joining chain



Secretory component

IgA molecule – dimeric

What does Immunoglobulin D (IgD) do?

- Immunoglobulin D (IgD) (1i) is an antibody isotype 1% of proteins in the plasma membranes of immature B-lymphocytes.
- Co-expressed with IgM (1i) on most mature B-cell membranes.
- Chiefly functions as an antigen receptor for naïve B-cells.
- Also IgD (like IgE) activates basophil and mast cells to produce anti-microbial factors.
- Monomeric structure; present in very low quantities (0.25% of plasma immunoglobulins.

What are features of IgE?

Immunoglobulin E (1pm, 2pm, 3w, 4i)

- Binds to allergens.
- Triggers mast cell degranulation.
- Primary defense against parasitic invasion.
- An excess of IgE is associated with the atopic triad (1i) (asthma, hay fever, eczema) and allergic reactions (type 1 hypersensitivity: fast-acting immune response mediated by IgE)
- Omalizumab, a monoclonal antibody, is used in treating severe allergy by means of neutralizing free IgE in the plasma.
- Monomeric structure.

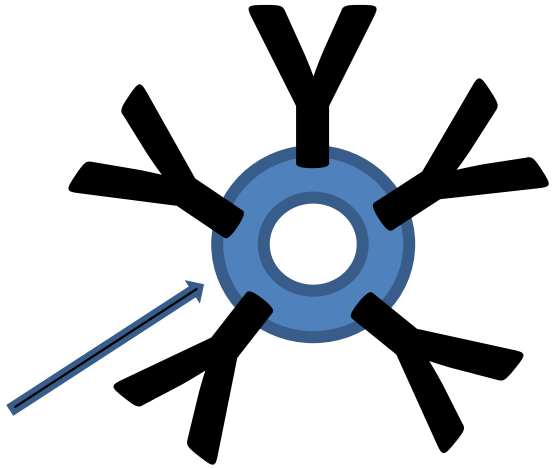
What is immunoglobulin G (IgG)?

- Immunoglobulin G (IgG) (1i) is the most common and all-purpose form of antibody (ca 75% of all plasma immunoglobulins are IgG).
- The main source of antibody-based immunity.
- The only immunoglobulin that crosses the placental barrier. It provides immune protection up until the age of approximately 6 months, when the infant's own immune system (should) be developed enough to take over.
- Monomeric structure.

What is immunoglobulin M (IgM)?

- Immunoglobulin M (IgM) (1i) is the first defense against pathogens until IgG levels rise.
- Bound to B-cell surface as a monomer, but secreted as a pentamer.
- Can bind to complement proprotein C1 (C1 complex) and activate the classical complement pathway.

IgM pentamer



Joining chain

What is B-cell class switching?

- B- cell class switching (1yt, 2yt) or isotype switching, is when a B-cell is stimulated (primarily by T_H cytokines) to produce immunoglobulins of a different class.
- Naïve B-cells produce IgM and IgG.
- Class-switching promotes the production of IgA, IgE, and IgG.
- By this mechanism, daughter plasma cells from a single activated B-cell can produce a range of immunoglobulin isotypes or subtypes.

The Complement Cascade

What is the complement cascade?

- A complement cascade (1i, 1a-i, 2yt, 3yt) is a series of ongoing activation in which each activated molecule activates the next (e.g., the "clotting cascade").
- Complement proteins are largely formed in the liver (but also tissue macrophages, blood monocytes, and GI/GU epithelial cells) and circulate in the bloodstream as inactive proproteins, together with corresponding inactive proteases.
- When the relevant proteases are stimulated, they cleave the complement proproteins, which under the influence of cytokines stimulates a cascade of activation.

What are the functions of the complement cascade?

- Opsonisation
- Chemotaxis
- Inflammation
- Lysis or apoptosis of pathogens and infected cells.

What are the three complement pathways (1, 2, 3)?

Three Complement Pathways (1i, 2i, 3i)

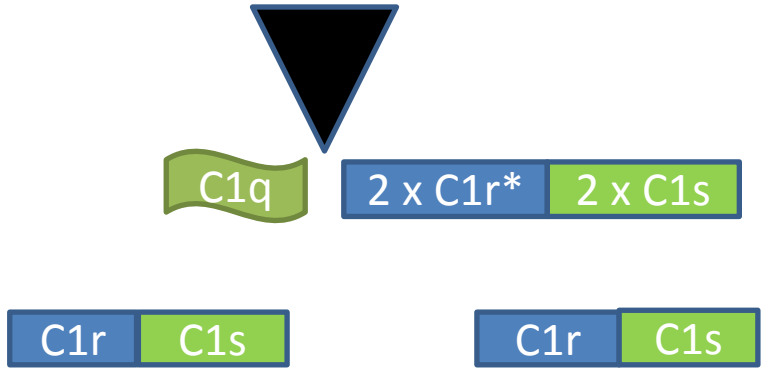
- *Classical pathway* (triggered when an antigen-IgM or – IgG complex binds to complement complex C1) (1w, 2rg, 3ow)
- *Alternative pathway* (C3 complex is continuously activated at a low level; the C3b fragment is normally continuously deactivated by factors H and I, but when it binds to a cell or pathogen, it is protected from deactivation)(1w, 2i, 3rg)
- *Lectin pathway* (similar to the classical, but triggered by binding of the mannose-binding lectin to mannose present on the pathogen's surface) (1w, 2i, 3i).

What happens in the classical pathway?

- 1) C1 complex = 1 molecule of C1q, 2 molecules of C1r, 2 molecules of C1s ($C1qr^2s^2$).
- 2) C1q binds to 1 (pentameric) IgM/antigen complex, 6 (monomeric) IgG/antigen complexes, or directly to pathogen surface (1i).
- 3) Binding changes C1q conformation, activating 2 C1r molecules, which then cleave 2 C1s.

The basic proprotein C1 structure

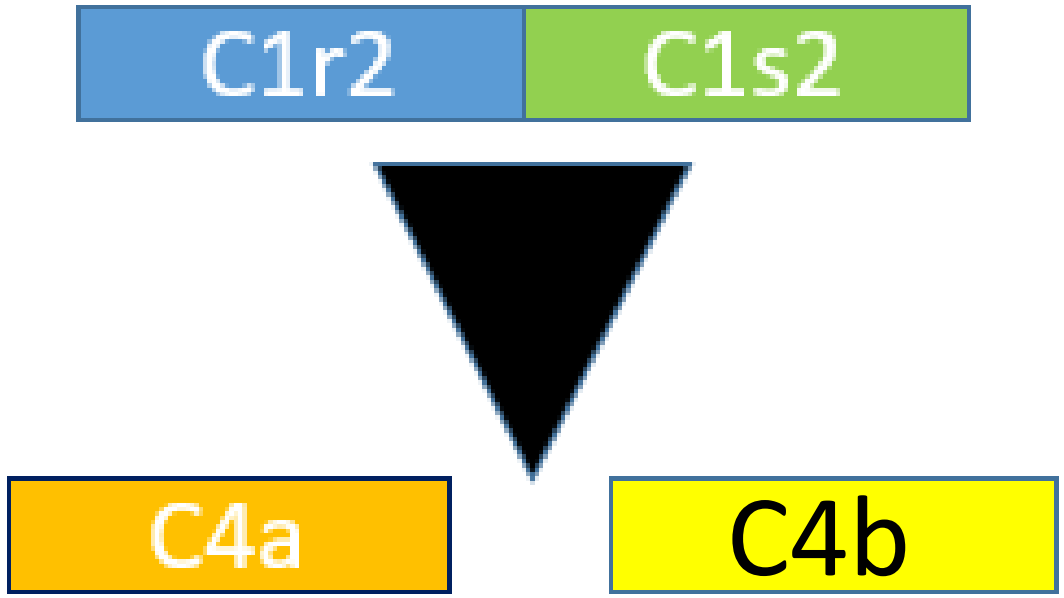
C1q binds to pentameric IgM complex (shown) or 6 monomeric IgG/antigen complexes, or directly to the surface of an antigen.



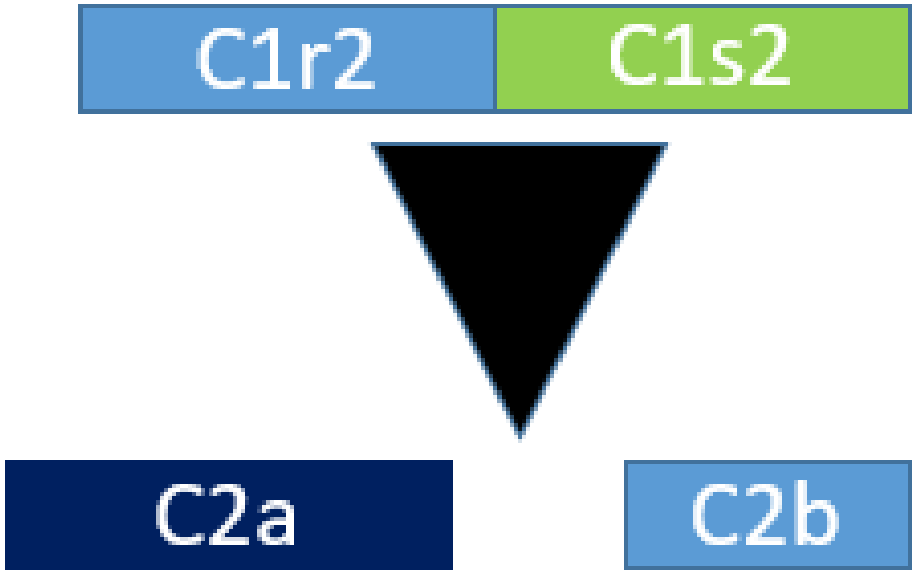
C1q changes configuration when bound, activating (*) 2 C1r molecules, which cleave off to form 2 C1rs complexes.

Classical Pathway (continued)

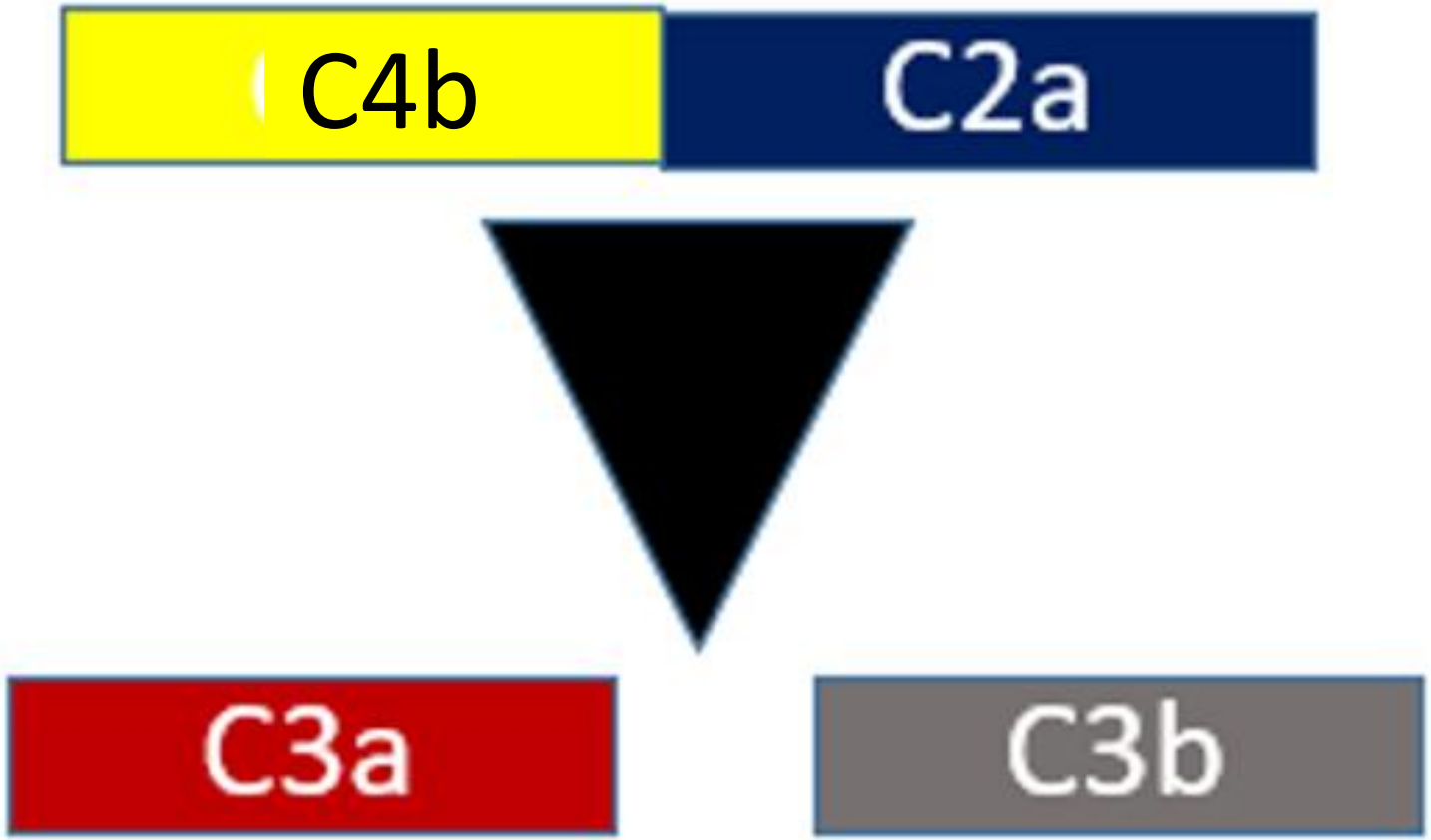
- **4) $C1r^2s^2$ cleaves C4 complex into C4a and C4b, then C2 complex into C2a and C2b.**
- **Note: there has been a change in nomenclature recently. Originally C2a was the name given to the smaller fragment and C2b to the larger one which binds to C4b. It is now more common for the larger C2 fragment to be called C2a and the smaller one C2b. However, some sources retain the older nomenclature, so that C3 convertase is sometimes described as C4b2b!**
- **5) C4b and C2a (larger fragment) bind into C4b2a complex, aka C3 convertase, triggering cleavage of C3 complex into C3a and C3b.**
- **6) C3b binds to C4b2a, producing C4b2a3b, aka C5 convertase.**



C1r2s2 cleaves C4 into C4a and C4b.



C1r2s2 cleaves C2 into C2a and C2b



C4b binds to C2a, forming C3 convertase and cleaving C3 into C3a and C3b.

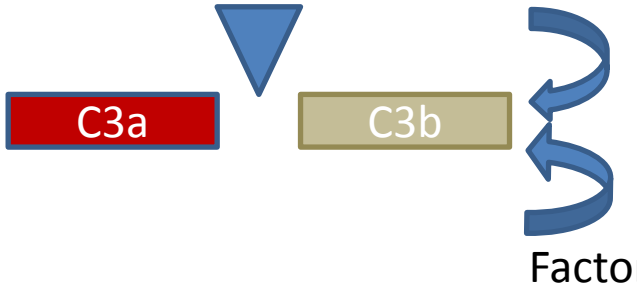
C3b binds to C4b2a, creating C5 convertase (C4b2a3b).

What happens in the alternative pathway?

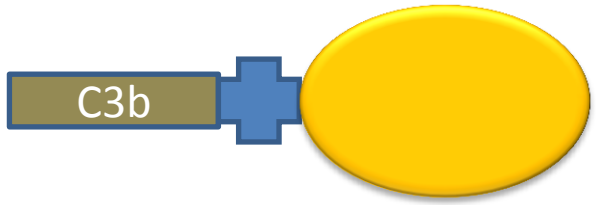
- Constitutional low-level cleavage of C3 complex; C3b normally deactivated by factors H and I.
- 1) Internal thioester of C3b binds covalently to amino or hydroxyl group on cell or pathogen surface, protecting it from H inactivation.
- 2) Bound C3b binds factor B = C3bB. Factor D enables cleavage into Ba and Bb.
- 3) Bb remains bound to C3b = C3bBb, aka alternative C3 convertase.

Alternative pathway (continued)

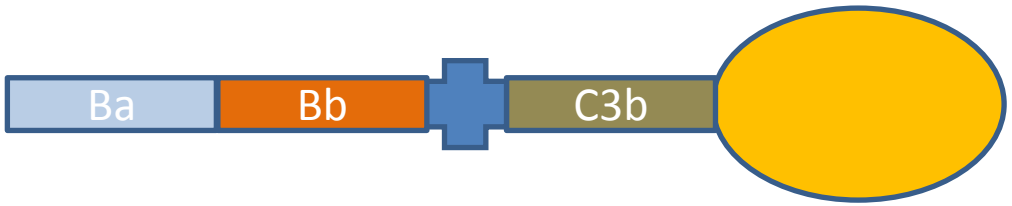
- 4) C3bBb binds stabilizing factor P. The amplification of C3 cleavage now commences; more C3b binds to the same surface, recruiting more D, B, and P, amplifying complement activation.
- 5) Alternative C3 convertase covalently binds another C3b = C3bBbC3bP, or alternative C5 convertase.



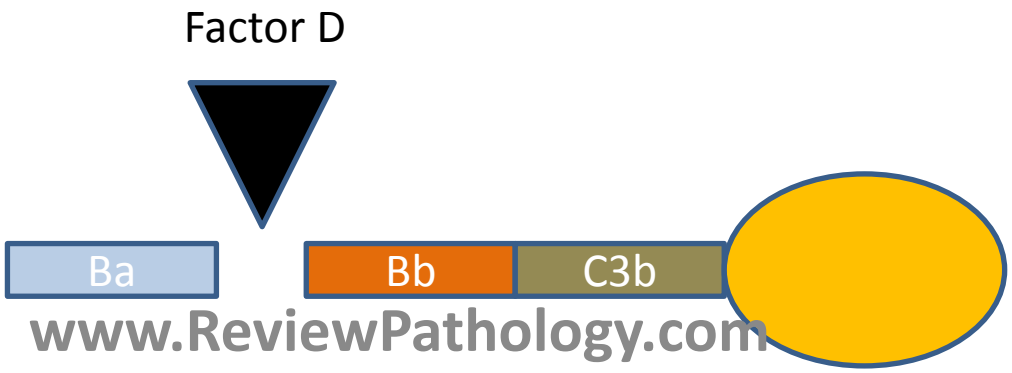
Low-level constitutional cleavage of C3;
C3b normally inactivated by factors H and I.



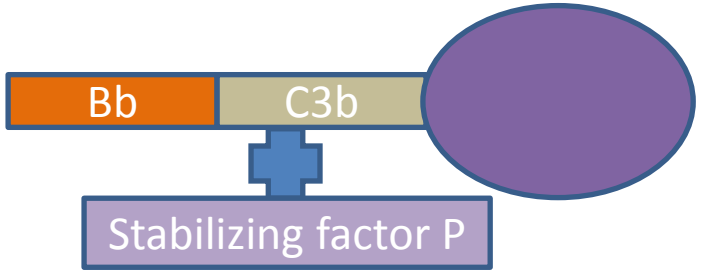
Internal thioester of C3b binds covalently to amino or hydroxyl on cell surface/pathogen, preventing inactivation by factor H.



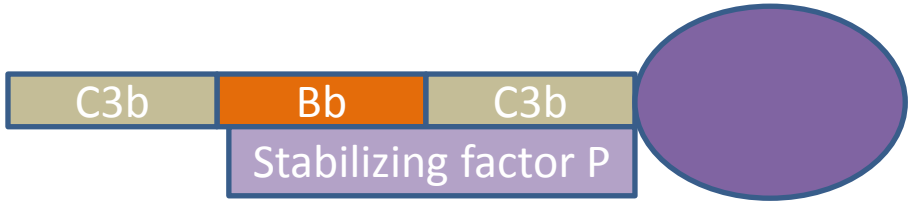
Bound C3b binds factor B (C3bB).



Factor D cleaves Ba from Bb; Bb remains bound, forming C3bBb (alternative C3 convertase).



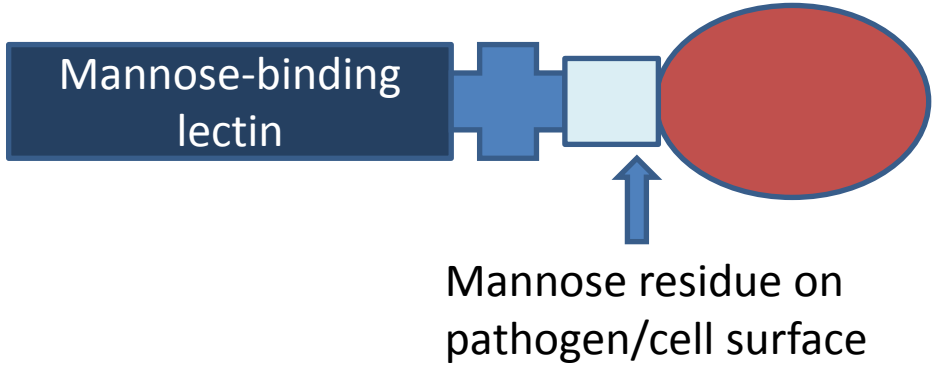
C3bBb binds stabilizing factor P. Amplification of C3 cleavage now begins.



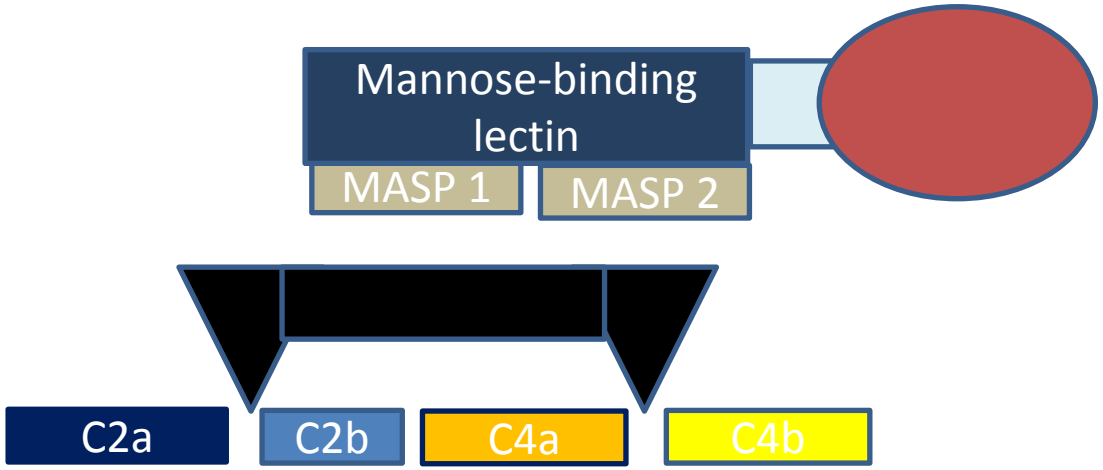
Alternative C3 convertase binds another C3b – C3bBbC3bP, or alternative C5 convertase.

What happens in the lectin pathway?

- 1) Mannose-binding lectin (MBL), resembling C1q, binds to mannose residue on cell or pathogen surface, or ficolins (lectin-type pattern recognition receptors) (1i, 2i, 3i, 4i) are activated.
- 2) This activates MBL-associated serine proteinases MASP-1 and MASP-2, which then split C4 (C4a, C4b) and C2 (C2a, C2b).
- 3) C4b and C2a bind to produce C4b2a/C3 convertase; the cascade continues as in the classical pathway.
- The crucial point of convergence for all pathways in the complement cascade is the cleavage of the C5 complex.



Mannose-binding lectin binds to mannose residue on pathogen or cell surface.

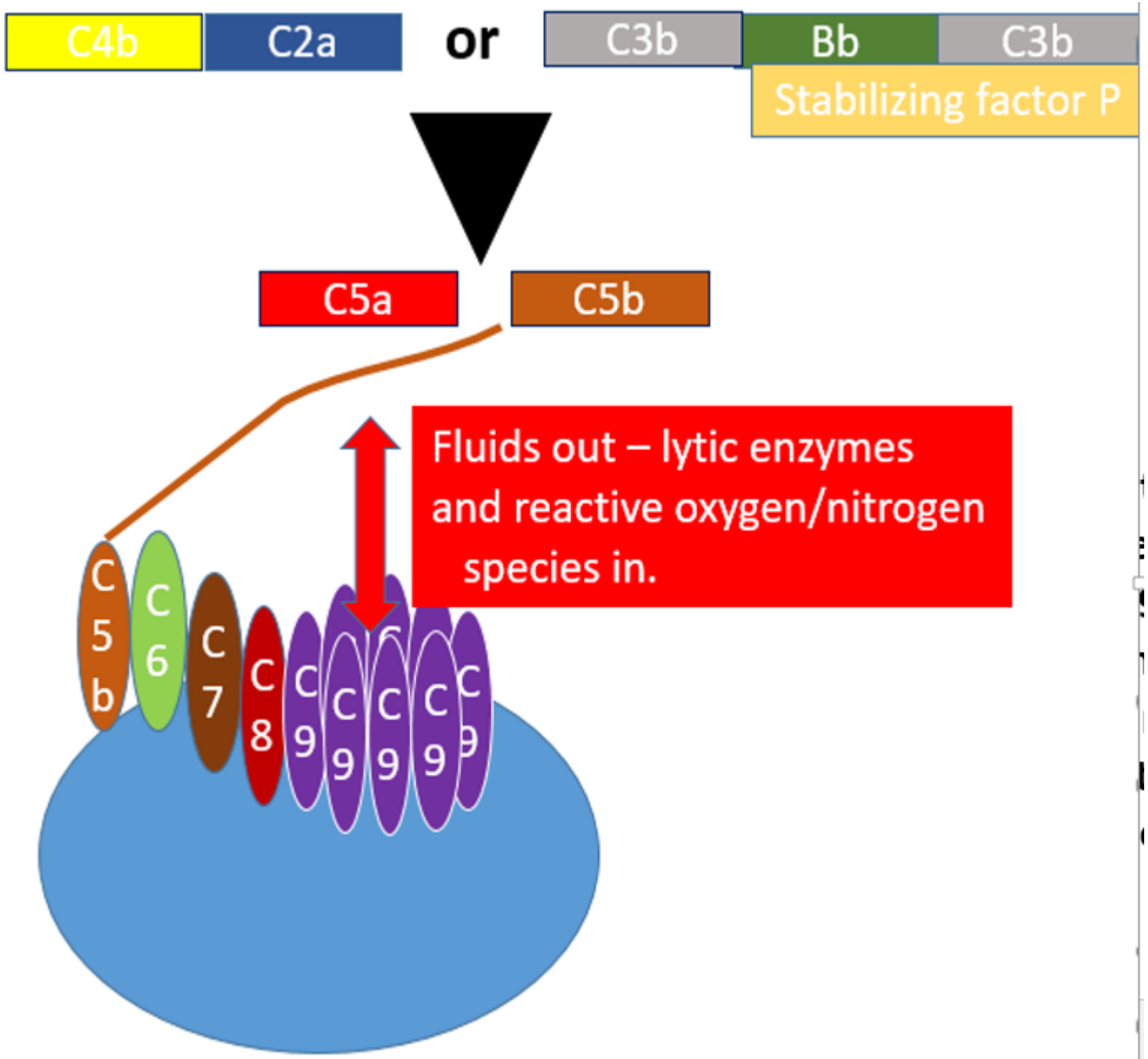


MASP 1 and MASP 2 serine proteinases split C2 and C4.

C4b and C2b bind to form C-3 convertase; the cascade proceeds as in the classical pathway.

How is the Membrane Attack Complex (MAC) formed? What does it do?

- 1) C5 complex is cleaved by either classical/lectin or alternative C5 convertase.
- 2) C5b gathers C6, C7, C8, and (multiple) C9, binding them into the Membrane Attack Complex (MAC) (1pm, 2pm, 3i, 4i). This forms a ring on the membrane of the target cell, opening a pore.
- 3) The MAC pores allow free diffusion of fluid in and out of the cell. This permits the inflow of reactive oxygen and nitrogen species and enzymes of dissolution. The simple increased diffusion from multiple pores also makes cellular survival impossible in and of itself.



Classical or alternative C5 convertase cleaves C5.

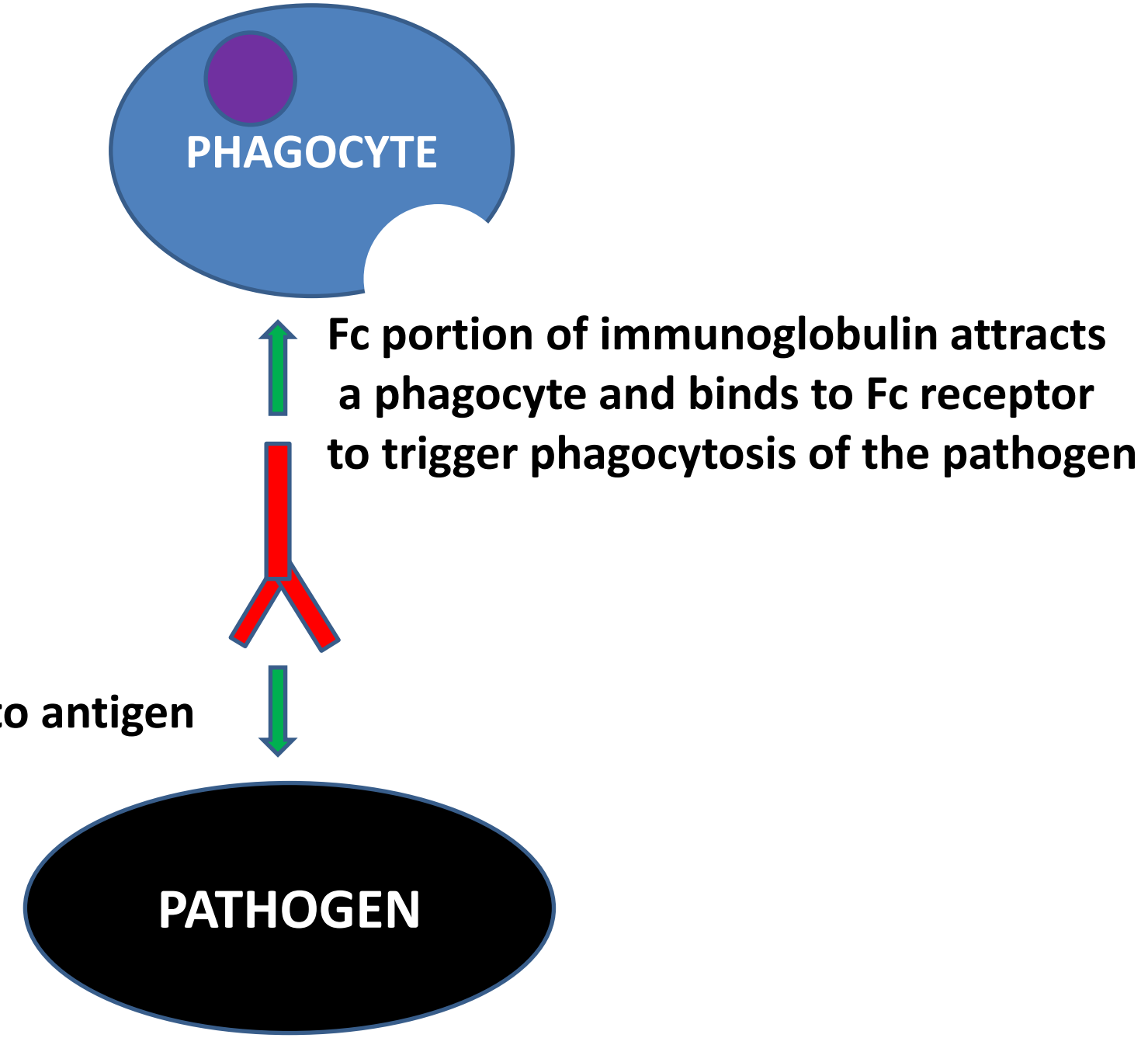
C5b binds to the membrane of the cell or pathogen and recruits C6, C7, C8, and multiple C9s to form the MAC (membrane attack complex). This opens a pore in the cell membrane through which fluids flow out and lytic enzymes and reactive oxygen and nitrogen species can enter.

What happens to the freed components of complement proteins?

- C3a, C4a, and C5a are all anaphylatoxins.
- All, particularly C5a, have powerful pro-inflammatory effects.
- C3a and C5a promote chemotaxis.
- C4a stimulates neutrophil promotion of pro-inflammatory cytokines.

What is opsonization?

- Opsonization (1i) is the term for antibody binding to an antigen so as to target the invading particle for phagocytosis.
- The resulting complex attracts phagocytes to the target. The antibody (Fc portion) also binds to an Fc receptor on the phagocyte to facilitate phagocytosis.
- Opsonization initiates the classical pathway of the complement cascade (watch video)



How does the complement cascade affect inflammation?

- Several freed fragments of complement proproteins are powerful inflammatory mediators.
- C3a, C4a, C5a – all anaphylatoxins (small inflammatory peptides)
- Stimulate:

  - Vasodilation

  - Vascular permeability

  - Degranulation of mast cells and basophils

  - Induce respiratory burst (reactive oxygen species production) in macrophages, neutrophils, and eosinophils.

Hypersensitivity Reactions

What are hypersensitivity reactions?

- Hypersensitivity reactions are the process of disease and tissue injury caused by immune responses.
- They may be reactions to external antigens, to microbes, or to inappropriate activation of the immune system against host proteins or tissues.

What is Type I hypersensitivity?

- Also known as ***immediate hypersensitivity***.
- Foreign antigen initially activates T_H2 cells; they produce IL- 4 which stimulates allergen-specific B cells to switch heavy-chain class to IgE production. (1i)
- Mast cells are essential for immediate hypersensitivity.
- IgE binds to mast cells.
- Foreign antigen interacts with IgE on sensitized mast cells.
- Mast cells degranulate, releasing histamine, adenosine, chemotactic factors, proteases. (1i, 2i, 3i)
- Mast cells also synthesize prostaglandins, leukotrienes, and inflammatory cytokines.

What are the characteristics of Type I hypersensitivity?

- Type I hypersensitivity ranges from local effects (urticaria, hay fever) to fatal systemic anaphylaxis (1pm).
- Common characteristics type 1 hypersensitivity include itching, urticaria (hives), skin erythema, mucus hypersecretion, and localized or systemic edema.
- Anaphylaxis is most often seen with parenteral and oral administration, and shows the common characteristics to extreme. Blood pressure drops rapidly due to systemic vasodilation; the patient is in danger of very rapid (within minutes) circulatory collapse and death unless treated (1pm).,
- Mediated by IgE.

What is Type II Hypersensitivity?

- Type II, or antibody-mediated, hypersensitivity is caused by antibodies (IgG and/or IgM) targeting cell surface or tissue antigens.
- These antigens may be intrinsic to the host, or drug metabolites.
- Antibodies:

- Activate the complement system (via the classical pathway, below).

- Target cells for phagocytosis.

- May interfere with cellular function by either blocking (as in myasthenia gravis) or overstimulating (as in Graves' disease).

What are some Type II Hypersensitivity Diseases?

- Immune thrombocytic purpura – antibodies target platelet membrane proteins; platelets are opsonized and phagocytosed; excessive bleeding occurs.
- Goodpasture syndrome – antibodies target basement membranes of renal glomeruli, pulmonary alveoli. Complement-mediated inflammation leads to nephritis and lung haemorrhage.
- Myasthenia gravis – antibodies target acetylcholine receptors in skeletal muscles. Receptors down-modulated; acetylcholine binding is inhibited; causes muscular weakness and paralysis.

What is Type III Hypersensitivity?

- Type III hypersensitivity is also called immune complex disease.
- Antigen/antibody complexes are formed in the circulation, then deposited in blood vessels and specific tissues.
- The most common sites are blood vessels (vasculitis), renal glomeruli (glomerulonephritis) and joints (arthritis).
- Inflammatory reaction occurs about 10 days after deposition.

How does immune complex deposition cause inflammation?

1. Immune complexes activate the complement cascade.
2. Immune complexes bind to and activate neutrophils and monocytes. Leukocytes begin to phagocytose immune complexes; they release various proinflammatory substances (vasoactive peptides, prostaglandins, chemotactic agents) and tissue-damaging digestive enzymes.
3. Platelet and Hageman factor activation causes microthrombi, which produce local ischaemia and further damage (as opposed to deficiencies, which cause bleeding diastheses.

What are some Type III hypersensitivities?

- Serum sickness – response to a foreign protein (early practice of using foreign serum for immunization, e.g., horse serum for an antidiptheria antibody)
- Systemic lupus erythematosus (SLE) – inappropriate antibody binding to nuclear antigens.
- Post-streptococcal glomerulonephritis – antigens from streptococcal cell walls collect in glomerular basement membranes.

What is Type IV Hypersensitivity?

- **Type IV Hypersensitivity , also known as *T-cell mediated hypersensitivity*.**
- **Can be either *delayed type hypersensitivity* (mediated by T_H1 CD4+ cells) or *direct cytotoxicity* (mediated by CD8+, aka "killer" T-cells).**
- **Includes a range of diseases, from simple contact dermatitis to type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis.**

What are the features of delayed-type hypersensitivity (DTH)?

- An initial exposure to the antigen causes CD4+ T_H1 cells to generate effector memory CD4+ cells.
- On subsequent exposures, the antigen is presented by antigen-presenting cells, activating the corresponding T_H1 cells.
- These cells produce interferon-γ, which activates macrophages, as well as other cytokines recruiting lymphocytes and monocytes to the site of the response.
- Multiple pro-inflammatory feedback loops lead to chronic DTH reactions unless the source is dealt with or the process halted medically.