SHEET NO. 12

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : **Doctor 2018**

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR : **Dr.Anas**

Humoral Immunity

Helper T Cell–dependent antibody responses to protein antigens:

- T cells are activated and they meet B cells, so they can form extra-follicular focus with short lived plasma cells.
- For a real antibody response (long lasting response), we must have a germinal center (inside the follicle) which includes: ***follicular T helper cells and follicular dendritic cells which help B cells to form long-lived plasma cells and long-lived B memory cells.***

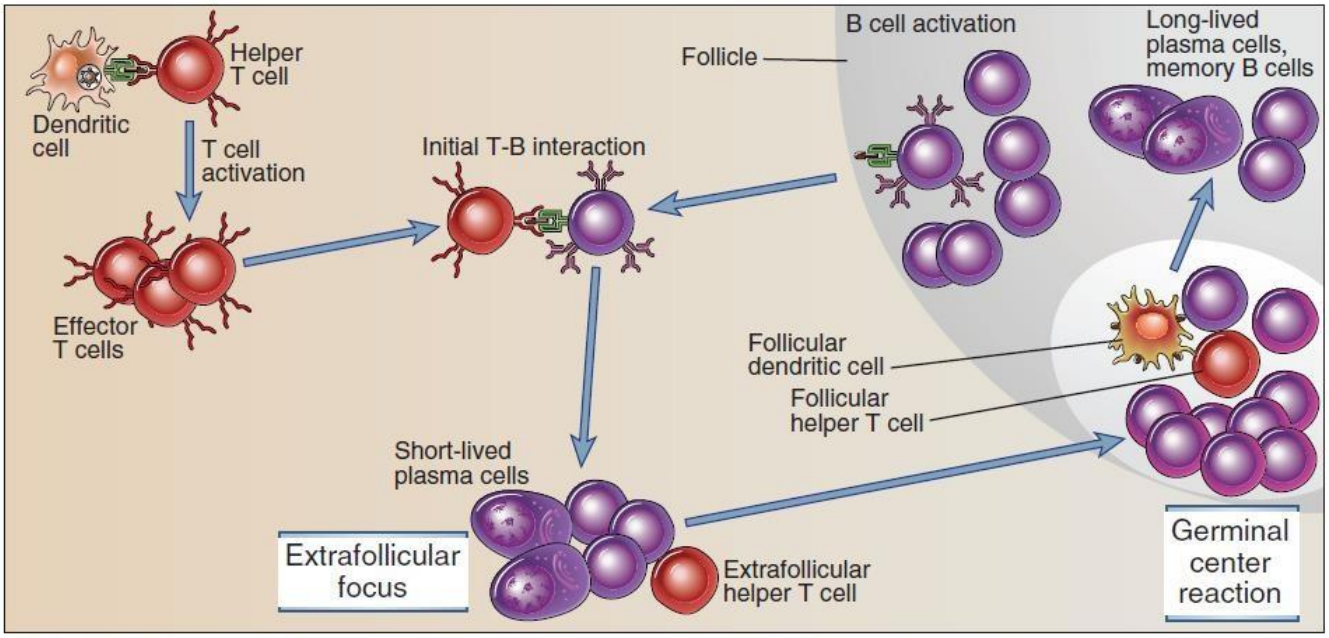


FIGURE 11–7 Sequence of events in humoral immune responses to T cell–dependent protein antigens. Immune responses are initiated by the recognition of antigens by B cells and helper T cells. The activated lymphocytes migrate toward one another and interact, resulting in B cell proliferation and differentiation. Restimulation of B cells by helper T cells in extrafollicular sites leads to early isotype switching and short-lived plasma cell generation. The late events occur in germinal centers and include somatic mutation and the selection of high-affinity cells (affinity maturation), additional isotype switching, memory B cell generation, and the generation of long-lived plasma cells.

- The first two processes that occur in the germinal center ***are affinity maturation and isotype switching.***
- B cell gets activated then goes back to the germinal center of the follicle for certain structural organization. Then they start replicating in the dark zone acquiring small mutations leading to changes in their receptors.
- After that, they migrate to the light zone where they encounter follicular dendritic cells to test their receptors by binding to antigens ***presented by follicular dendritic cells***. (remember,
  follicular dendritic cells are bound to opsonized antigens by their complement receptors ***CR1 and CR2***).

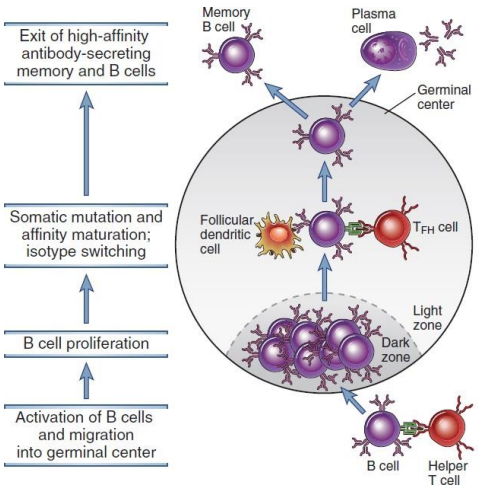


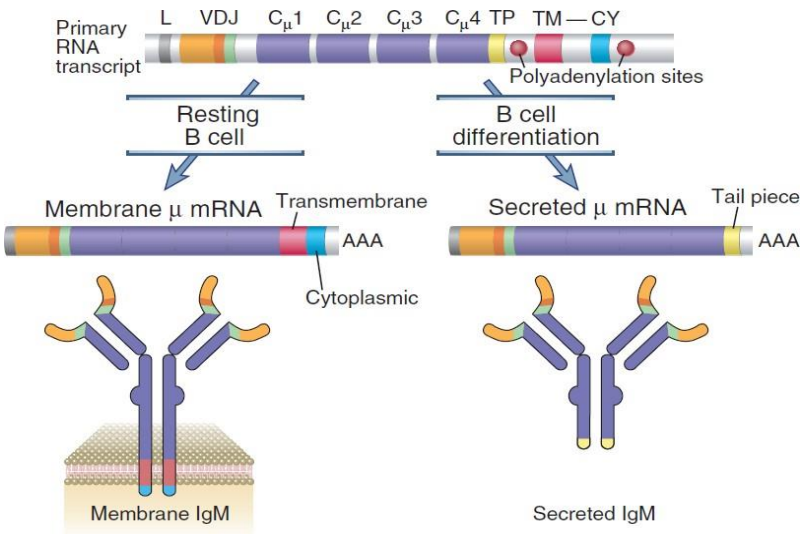
FIGURE 11–12 The germinal center reaction in a lymph node. B cells that have been activated by T helper cells at the edge of a primary follicle migrate into the follicle and proliferate, forming the dark zone of the germinal center. Germinal center B cells undergo extensive isotype switching. Somatic hypermutation of Ig V genes occur in these B cells, and they migrate into the light zone, where they encounter follicular dendritic cells displaying antigen and T_{FH} cells. B cells with the highest affinity Ig receptors are selected to survive, and they differentiate into antibody-secreting or memory B cells. The antibody-secreting cells leave and reside in the bone marrow as long-lived plasma cells, and the memory B cells enter the recirculating pool.

- If the receptor binds good, the cell will survive and continues to differentiate into plasma or memory cell. But if the receptor doesn't bind or binds with bad quality, the cells will undergo apoptosis because this region is full of ***cytokines like IL-21*** which induces apoptosis if the cell was not rescued (by antigen binding).
- Also, isotype switching occurs by changing naïve B cell receptor from IgM or IgD into IgA, IgG or IgE plasma and memory cells (depending on certain cytokines).

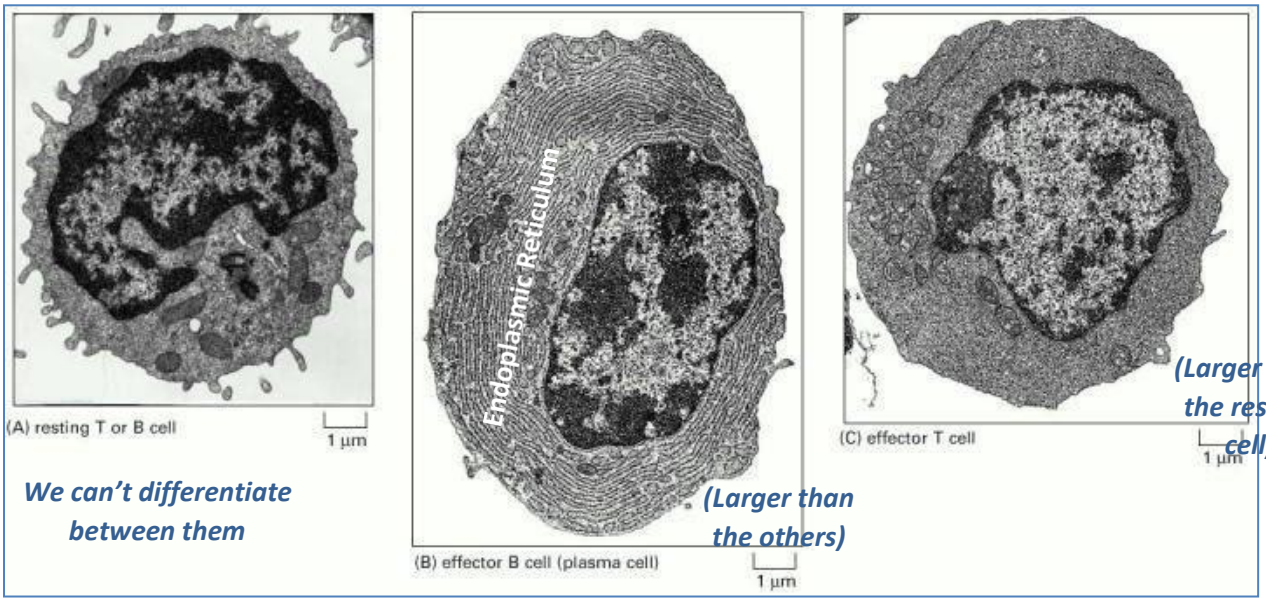
- Plasma cells are morphologically distinct***, terminally differentiated*** (can't go back and do isotype switching for example) B cells committed to abundant ***antibody production.***
- They are generated after the activation of B cells through signals from the BCR, CD40, TLRs, and other receptors including cytokine receptors.
- There are 2 types of plasma cells:
  - ***Short-lived plasma cells*** (live for 2 or 3 months) are generated during ***T-independent (like LPS response)*** responses and early during T cell– dependent responses in extrafollicular B cell foci. These cells are generally found in ***secondary lymphoid organs*** and in ***peripheral nonlymphoid tissues (like the skin). Note: a small amount of memory cells may be generated during T-independent response.***
  - ***Long-lived plasma cells*** (for life time) are generated in ***T-dependent*** germinal center responses to protein antigens. Signals from the B cell antigen receptor and IL-21 cooperate in the generation of plasma cells, acquire the ability to home to the ***bone marrow***, where they are maintained by cytokines of the ***BAFF family (B Cell activating factor of TNF family)*** which keep giving them survival signals. They set in the bone marrow for 20-30 years and they never go out again.

- Typically, 2 to 3 weeks after immunization with a T cell–dependent antigen, the ***bone marrow*** becomes ***a major site of antibody production*****.** That's why if you test different people you will find different pool of antigens depending on the antigens that they have encountered.
- Plasma cells in the bone marrow may continue to secrete antibodies for months or even years after the antigen is no longer present.
- It is estimated that almost ***half the antibody in the blood of a healthy adult is produced by long*****-lived plasma cells** and is ***specific*** for antigens that were encountered in the past. The other half is short lived from T-independent response.
- Secreted antibodies enter the circulation and mucosal secretions, but mature plasma cells ***do not recirculate.***

- Changes during differentiation of b cells include:
  - 1-the cell ***enlarges dramatically***, and the ratio of cytoplasm to nucleus also undergoes a striking increase.
  - 2- The ***endoplasmic reticulum becomes prominent (to help in the production of antibodies)***, and the cell is transformed into a ***secretory cell*** that bears little or no resemblance to a B cell.
  - 3-The change in Ig production from the ***membrane form*** (characteristic of B cells) to the ***secreted form*** (in plasma cells).



Notice how the transmembrane (TM) part is only translated in the membrane Immunoglobulins (of naïve B cells or activated B cells that don't secrete Igs) to help them be incorporated into the membrane because it is hydrophobic.



We can't differentiate between them

(Larger than the others)

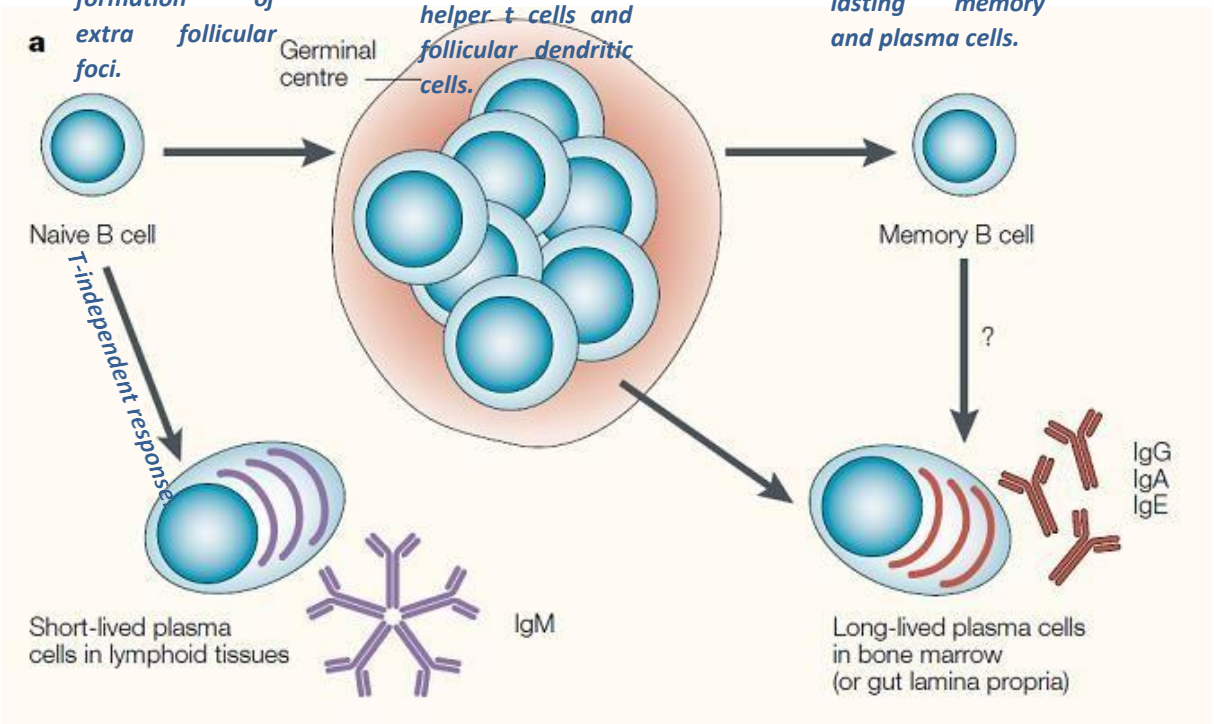
(Larger than the resting cell)

they all have different nucleus to cytoplasm.

T-dependent response and formation of extra follicular foci.

They later on form the germinal center with the help of follicular helper t cells and follicular dendritic cells.

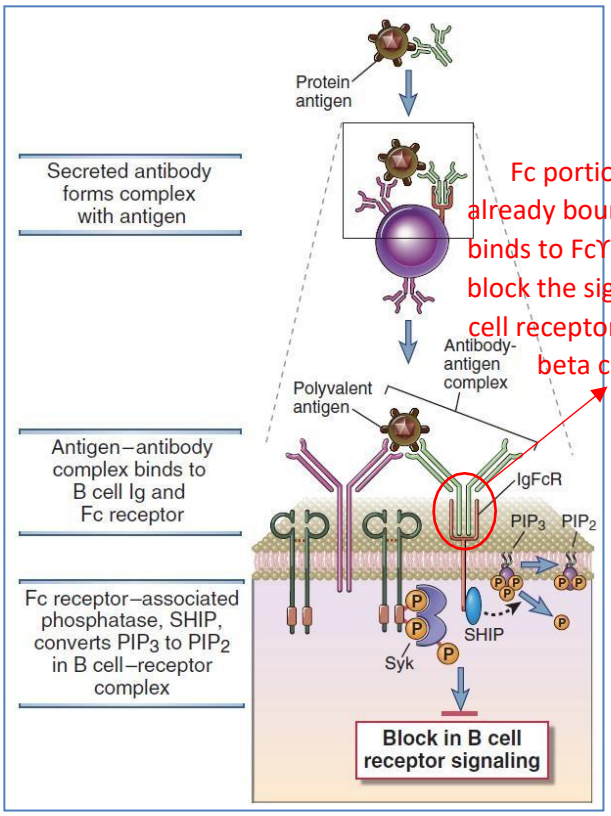
Formation of long-lasting memory and plasma cells.



- Some of the antigen-activated B cells emerging from germinal centers acquire the ability to survive for long periods (by expressing high levels of the antiapoptotic protein Bcl-2), apparently without continuing antigenic stimulation, these are ***memory cells.***
- Memory cells have undergone some affinity maturation, so they have better receptors than naïve cells even if they recognize the same antigen.
- Some memory B cells ***may remain in the lymphoid organ*** where they were generated, whereas ***others exit germinal centers and recirculate (same as naïve cells as they look to encounter the antigen again)*** between the blood and lymphoid organs.
- They are produced in T cell dependent responses and usually emerge in parallel with ***memory helper T cells.***
- The production of large quantities of ***isotype-switched, high-affinity*** antibodies is greatly accelerated ***after secondary exposure*** to antigens, because they don't have to repeat the cycle and go to the extra follicular foci, germinal center, isotype switching and so on.
- After ***re-encountering*** the specific antigen, they are able to ***reactivate very quickly***, ***propagate themselves (because they are not terminally differentiated,*** create ***plasma cells*** and ***re-enter germinal centers*** to ***improve affinity*** **(*more affinity maturation*)** of their antibodies.

Antibody feedback:

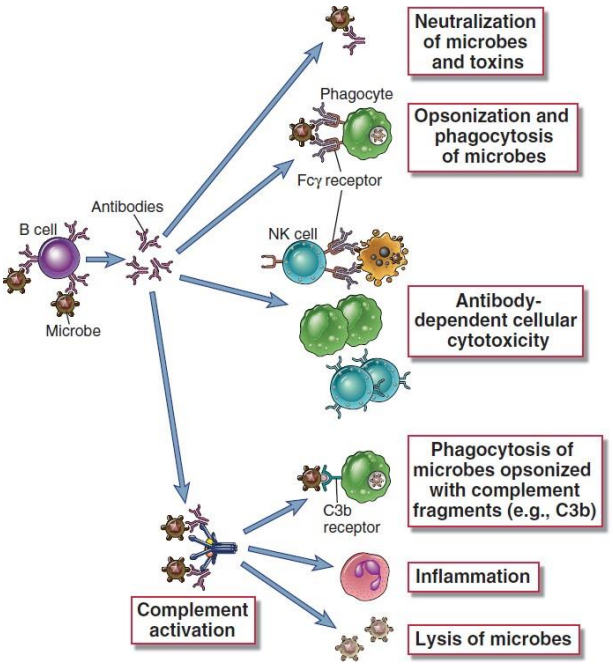
- Secreted antibodies ***inhibit continuing B cell activation*** by forming antigen-antibody complexes that simultaneously bind to antigen receptors and inhibitory ***Fcγ*** receptors on antigen-specific B cells.
- The antigen-antibody complexes simultaneously interact with the antigen receptor (through the antigen) and with ***FcγRIIB*** (through the antibody), and this brings the ***inhibitory phosphatases*** close to the antigen receptors whose signaling is blocked.
- This occurs as a feedback mechanism to stop the B cells from producing more antibodies.



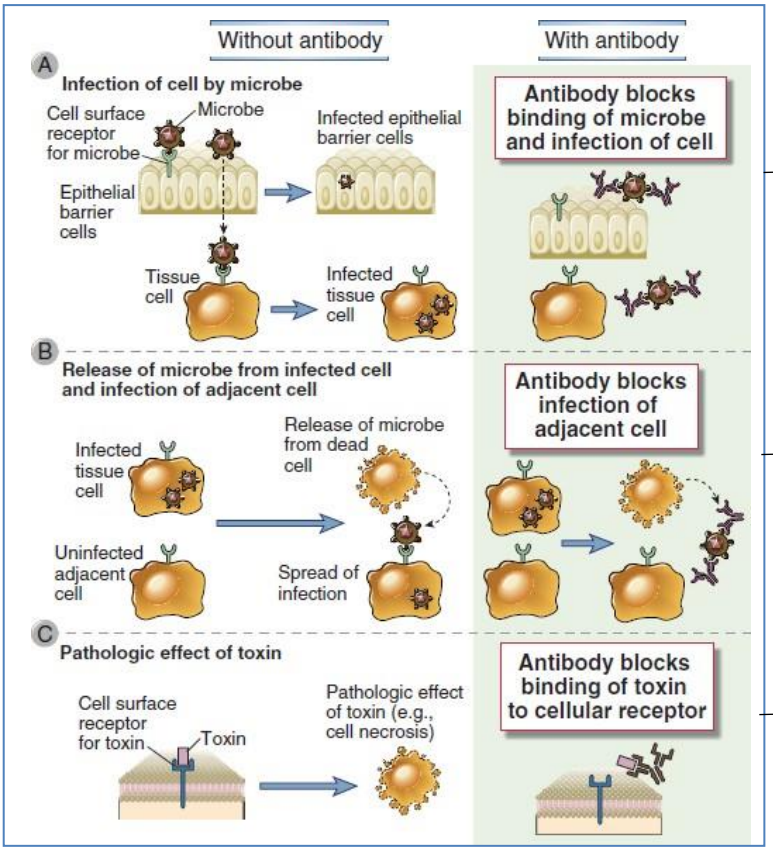
Fc portion of the already bound antibody binds to FcϒR receptor to block the signal of the B cell receptor (alpha and beta chains)

Effector mechanisms of humoral immunity:

- ***Antibodies, complement system and the antimicrobial peptides*** are the components of the humoral immunity.
- Functions of antibodies against bacteria and viruses:



1) Neutralization of microbes and toxins:



Blocking the primary infection by binding to the microbial antigens which they use to internalize into cells.

Limiting the infection by inhibiting the spread to adjacent cells with the same mechanism in A.

Blocking the binding of AB toxins.

Remember: A (active unit) and B (binding unit).

2) Opsonization and phagocytosis of microbes:

- IgG subtypes that bind best to Fc receptors (IgG1 and IgG3) are the most efficient opsonins for promoting phagocytosis. Binding of ***FcγRI (fragment crystallizable gamma receptor type 1)*** receptors on phagocytes to multivalent antibody-coated particles leads to engulfment of the particles and ***the activation of phagocytes (by certain signals).***
- Activation leads to:

➢ Production of the ***enzyme phagocyte oxidase***, which catalysis the intracellular generation of ***reactive oxygen species*** that are cytotoxic for phagocytosed microbes. This process is called ***the respiratory burst (oxidative burst).***

➢ Activation of an enzyme called ***inducible nitric oxide synthase (iNOS),*** which triggers the production of nitric oxide that also contributes to the killing of pathogens.

➢ Secretion ***of hydrolytic enzymes*** and ***reactive oxygen intermediates*** into the external milieu that are capable of killing extracellular microbes) too large to be phagocytosed (prepare the cell to fight extracellular microbes also. The same toxic products ***may damage tissues***.

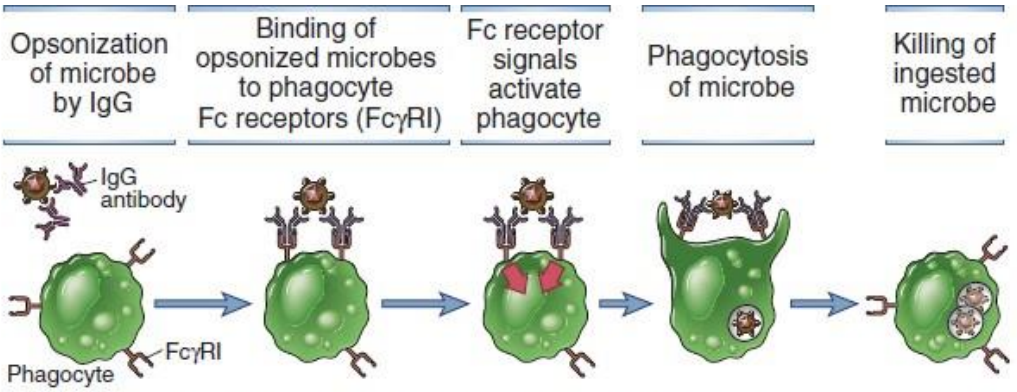


FIGURE 12–4 Antibody-mediated opsonization and phagocytosis of microbes. Antibodies of certain IgG subclasses bind to microbes and are then recognized by Fc receptors on phagocytes. Signals from the Fc receptors promote the phagocytosis of the opsonized microbes and activate the phagocytes to destroy these microbes. The microbicidal mechanisms of phagocytes are described in Chapters 4 (see Fig. 4-13) and 10 (see Fig. 10-7).

3) Antibody dependent cellular cytotoxicity:

- Natural killer (NK) cells and other leukocytes bind to antibody-coated cells (infected cells) by Fc receptors and destroy these cells. This process is called ***antibody-dependent cellular cytotoxicity (ADCC).***
- Engagement of ***FcγRIII*** هاض ثالث واحد انذكر بالمحاضرة ... اذا قادر تعرفهم فأمورك بالسليم في المحاضرة إن شاء الله😊 by antibody-coated target cells activates the NK cells to synthesize and secrete cytokines such as ***IFN-γ*** as well as to discharge the contents of their granules (perforins and granzymes), which mediate the killing functions of this cell type (this is a stimulatory signal for NK cells in contrast to the presence of MHC-1 which is an inhibitory signal).

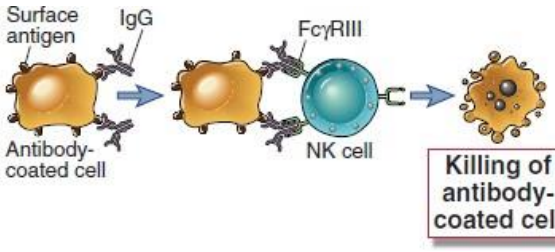


FIGURE 12–5 Antibody-dependent cell-mediated cytotoxicity. Antibodies of certain IgG subclasses bind to cells (e.g., infected cells), and the Fc regions of the bound antibodies are recognized by an Fcγ receptor on NK cells. The NK cells are activated and kill the antibody-coated cells. Presumably, NK cells can lyse even class I MHC–expressing targets when these target cells are opsonized because the Fc receptor–mediated stimulation may overcome the inhibitory actions of class I MHC–recognizing NK cell inhibitory receptors (see Chapter 12).

- This is used as a mechanism to fight tumors by using monoclonal antibodies against important tumors antigens. ***Epidermal growth factor receptor (EGFR)*** which is over expressed in many epithelial tumors, is a target of the monoclonal antibody ***Cetuximab***, this will block the signaling of EGFR and this further more activates antibody dependent cellular cytotoxicity (NK cells).

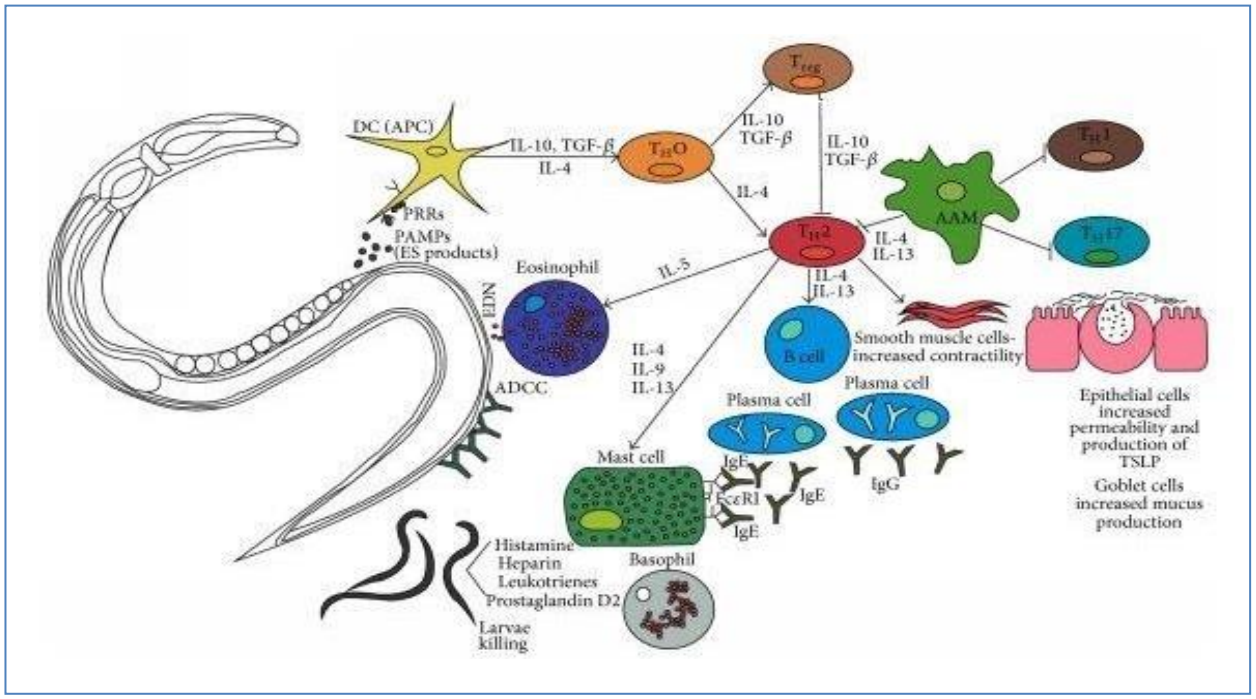
4) Activation of the complement system.

Antibody-Mediated Clearance of Helminths:

- ***Antibodies, mast cells, and eosinophils*** function with together to mediate the expulsion and killing of some helminthic parasites. Helminths (worms) are too large to be engulfed by phagocytes, and their integuments are relatively resistant to the microbicidal products of neutrophils and macrophages.

- ***IgE, IgG, and IgA*** antibodies that coat helminths can bind to Fc receptors on eosinophils and cause the ***degranulation of these cells***, releasing the ***major basic protein***, *a* ***toxic cationic protein (works probably by producing holes in the cell wall)***, present in the granules of eosinophils. Other eosinophil granule contents also aid in killing the parasites.

- ***IgE antibodies*** that recognize antigens on the surface of the helminths may initiate local ***mast cell degranulation (release of histamine, heparin and leukotrienes)*** through the ***high-affinity IgE receptor***. Mast cell mediators may induce ***bronchoconstriction and increased local motility (gastric and GI motility)***, contributing to the ***expulsion*** of worms. Mast cell contents also kill the larvae.



Certain antigens are secreted by the helminths ➔ recognized by APCs ➔ activation of helper T cells ➔ secretion of cytokines (like IL-4) which causes isotype switching of B cells into IgE plasma cells ➔ IgE antibodies bind to FcϵR and to antigens on the surface of the parasite ➔ eosinophils use their high affinity receptors to recognize the bound IgE antibodies and then they degranulate ➔ release of major basic protein.

- Some helminthic products may also activate immunomodulatory pathways and inhibit the immune response. An example is the activation of the alternatively activated macrophage (AAM) which is involved in the immune regulation and inhibition by the production of certain cytokines (like IL-10 and TGF-β). This can be used as ***therapeutic immunomodulators*** to control the immune response in hyperactivity of the immune system and autoimmune diseases.

Revision of Fragment Crystallizable (Fc) receptors:

TABLE 12–3 Fc Receptors

FcR	Affinity for Immunoglobulin	Cell Distribution	Function
FcγRI (CD64)	High ($K_d < 10^{-9}$ M); binds IgG1 and IgG3, can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
FcγRIIA (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
FcγRIIB (CD32)	Low ($K_d > 10^{-7}$ M)	B lymphocytes	Feedback inhibition of B cells
FcγRIIC (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils, NK cells	Phagocytosis, cell activation
FcγRIIIA (CD16)	Low ($K_d > 10^{-6}$ M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
FcγRIIIB (CD16)	Low ($K_d > 10^{-6}$ M); GPI-linked protein	Neutrophils	Phagocytosis (inefficient)
FcεRI	High ($K_d > 10^{-10}$ M); binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
FcεRII (CD23)	Low ($K_d > 10^{-7}$ M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
FcαR (CD89)	Low ($K_d > 10^{-6}$ M)	Neutrophils, eosinophils, monocytes	Cell activation?

GPI, glycophosphatidylinositol; NK, natural killer.

Revision of antibodies functions:

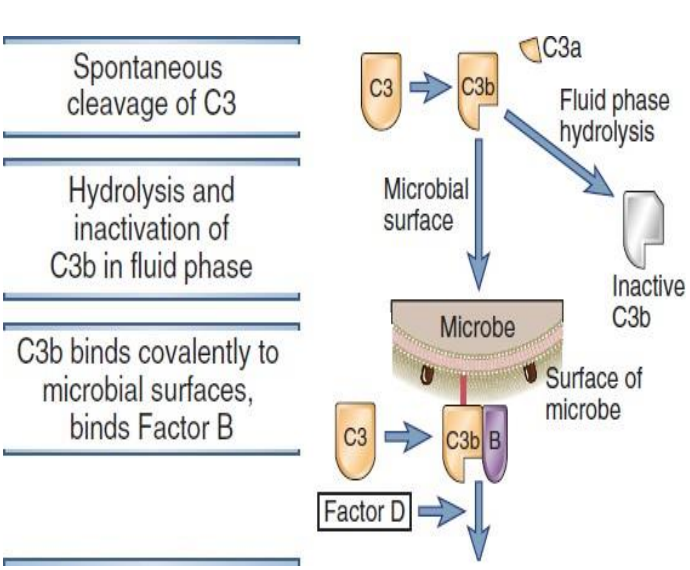
Some cells may still secrete IgM antibodies after isotype switching.

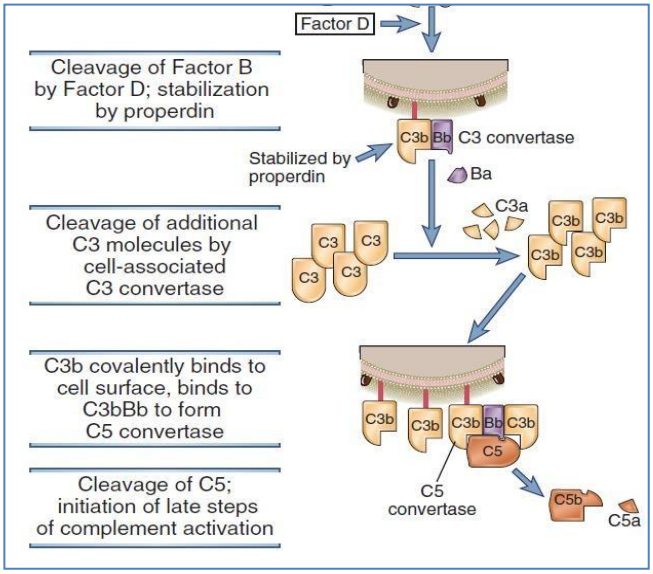
TABLE 12–1 Functions of Antibody Isotypes

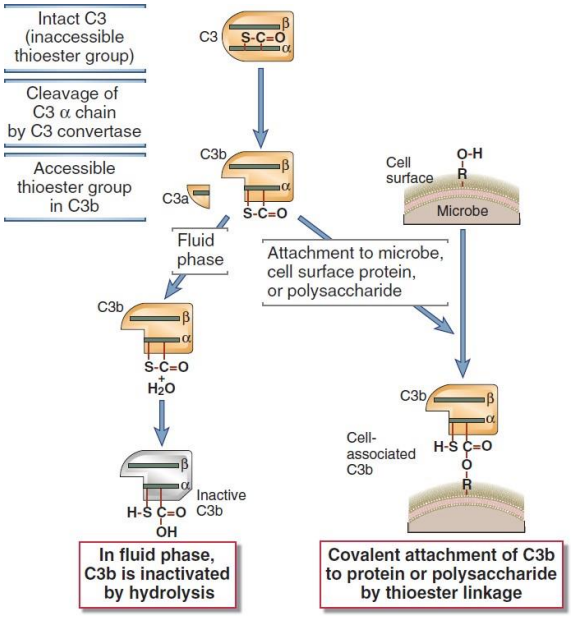
Antibody Isotype	Isotype-Specific Effector Functions
IgG	Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells Neonatal immunity: transfer of maternal antibody across the placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement Antigen receptor of naive B lymphocytes*
IgA	Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes*

*These functions are mediated by membrane-bound and not secreted antibodies.

Revision of complement system which is an important part of humoral immunity:







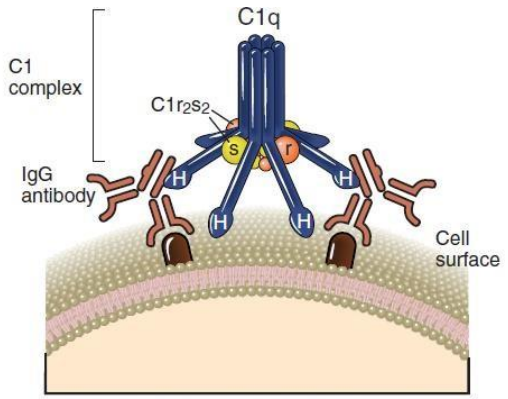


FIGURE 12–10 Structure of C1. C1q consists of six identical subunits arranged to form a central core and symmetrically projecting radial arms. The globular heads at the end of each arm, designated H, are the contact regions for immunoglobulin. C1r and C1s form a tetramer composed of two C1r and two C1s molecules. The ends of C1r and C1s contain the catalytic domains of these proteins. One $C1r_2s_2$ tetramer wraps around the radial arms of the C1q complex in a manner that juxtaposes the catalytic domains of C1r and C1s.

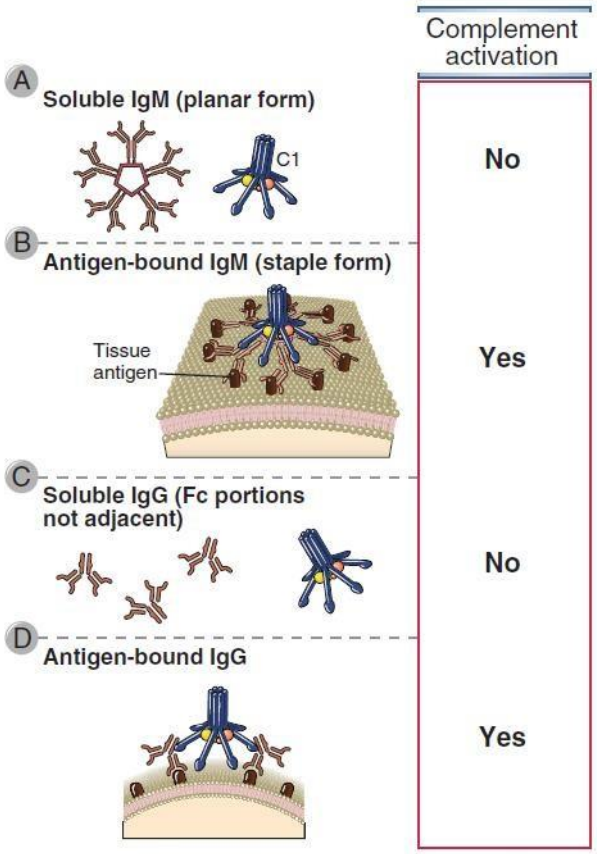


FIGURE 12–11 C1 binding to the Fc portions of IgM and IgG. C1 must bind to two or more Fc portions to initiate the complement cascade. The Fc portions of soluble pentameric IgM are not accessible to C1 **(A)**. After IgM binds to surface-bound antigens, it undergoes a shape change that permits C1 binding and activation **(B)**. Soluble IgG molecules will also not activate C1 because each IgG has only one Fc region **(C)**, but after binding to cell surface antigens, adjacent IgG Fc portions can bind and activate C1 **(D)**.

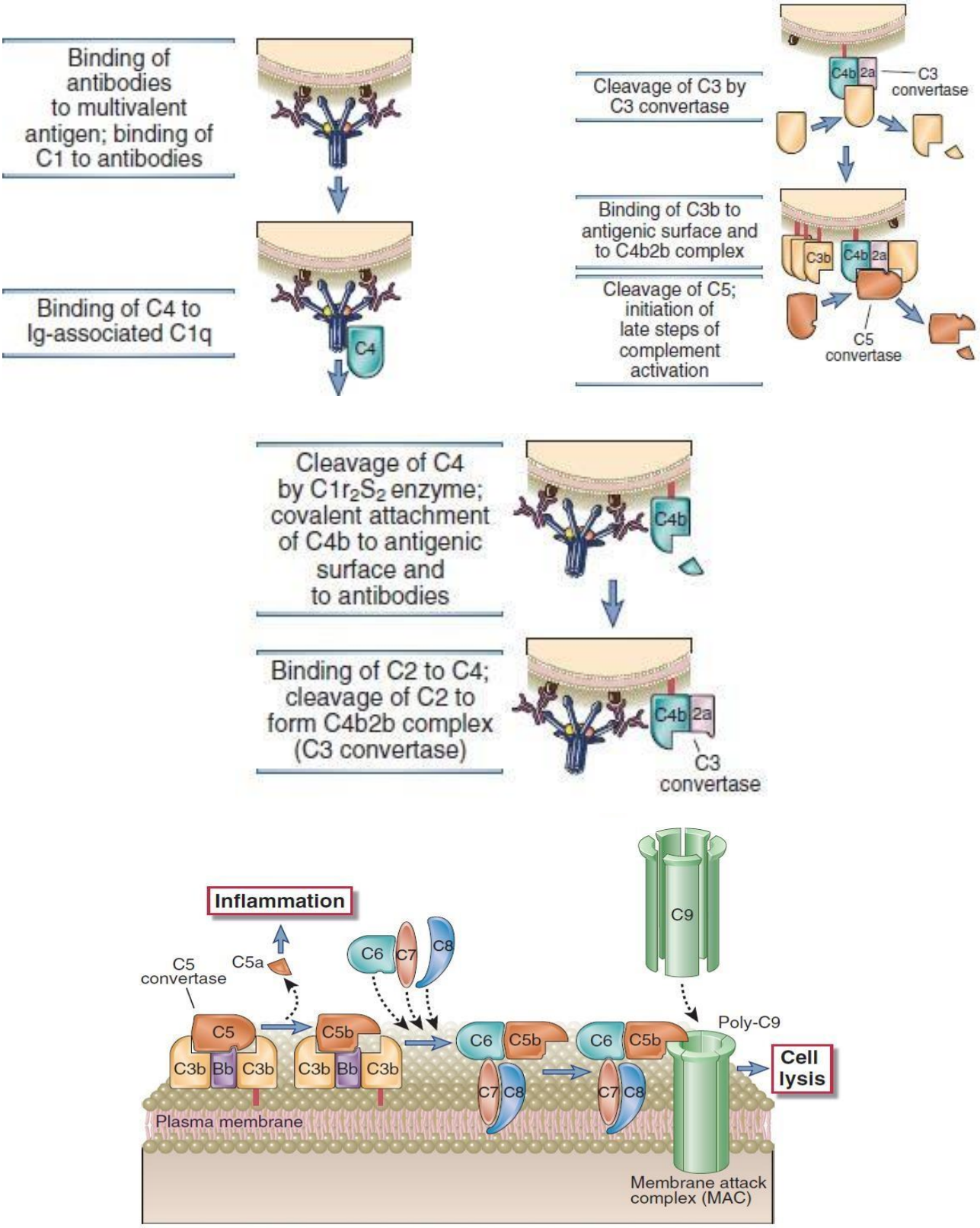


FIGURE 12–12 Late steps of complement activation and formation of the MAC. A schematic view of the cell surface events leading to formation of the MAC is shown. Cell-associated C5 convertase cleaves C5 and generates C5b, which becomes bound to the convertase. C6 and C7 bind sequentially, and the C5b,6,7 complex becomes directly inserted into the lipid bilayer of the plasma membrane, followed by stable insertion of C8. Up to 15 C9 molecules may then polymerize around the complex to form the MAC, which creates pores in the membrane and induces cell lysis. C5a released on proteolysis of C5 stimulates inflammation.

Good luck

Feel free to contact us for any misconception ;)

لا تنسوا والدة زميلنا جعفر الزبن من صالح دعائكم