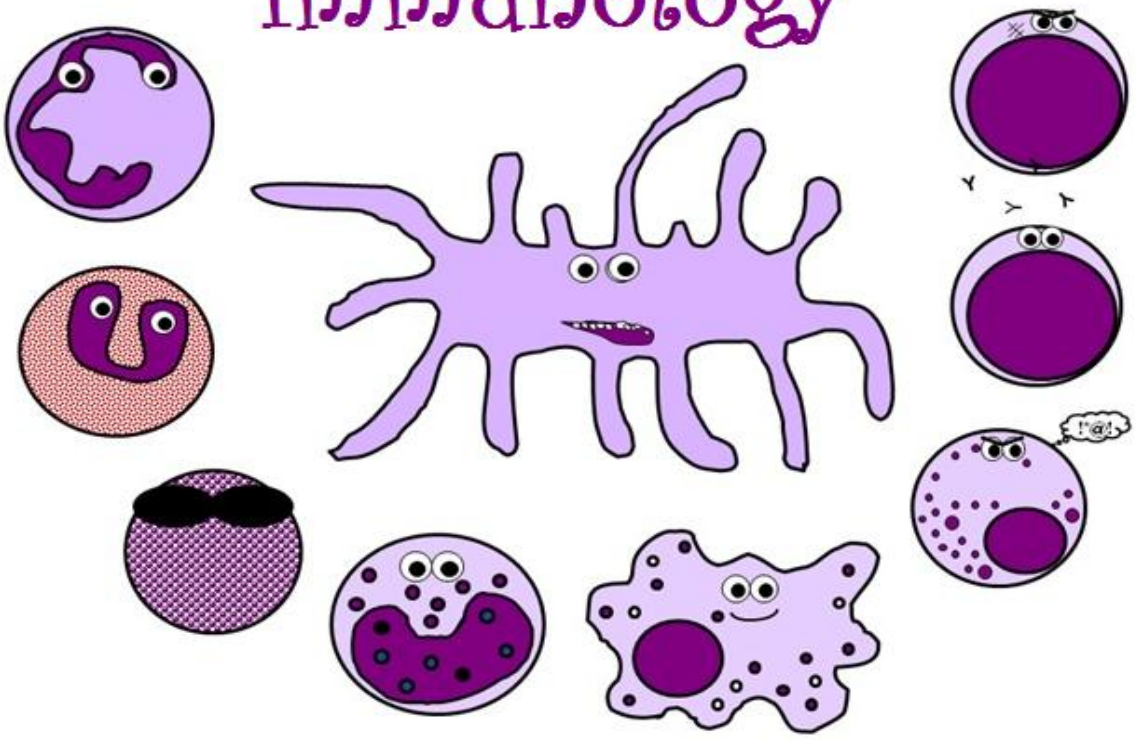
Immunology



◉Sheet ○Slides

Number: 2

Subject: Innate immune system

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Introduction :

- Hope fully you'll enjoy the sheet ,it's supposed to be fun, try to understand it 100%
- The recommended book is (cellular and molecular immunology, 8th edition)
- there are two types for immune system :
  - ✓ **Innate immune system** (non- specific); a very old system that presents in all living creatures ,and is responsible for fighting the foreign bodies instantly without being specific to any of them, but being able to detect the pathogens that entering our bodies, and end the infection, or at least buying some time so that the adaptive system will be activated and will handle the infection.

  - ✓ **Adaptive immune system**: B-Cells & T-Cells.

Innate Immune System

In labs , when we put an e-coli bacteria in a flask using a special medium, we'll find after some time that the medium became turbid, due to the short doubling time of E-coli. This logarithmic growth **won't** occur in our bodies because of the fast response of the innate immune system.

innate immune system has three components :

1) **Complement system:** protein products , mostly made in liver.

2) **Professional phagocytes**: Macrophages & Neutrophils.

3) **Natural Killing cells** "**NK**".

complement system:

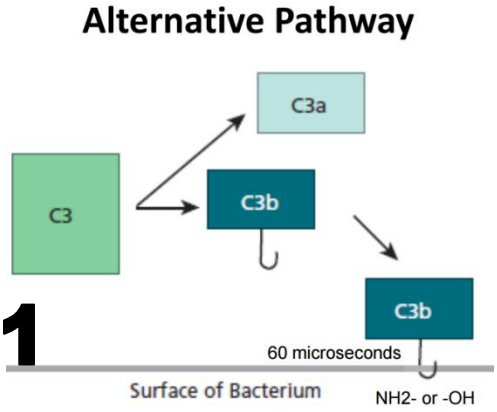
Is made of 20 types of proteins which will work together to destroy the invaders, they have direct abilities to kill the pathogens , in addition they can be a signaling molecule that'll inform other immune cells and recruit them in attacking those microbes.

The importance of the innate immune system is shown by being developed in the first trimester of pregnancy which means it's **critical**.

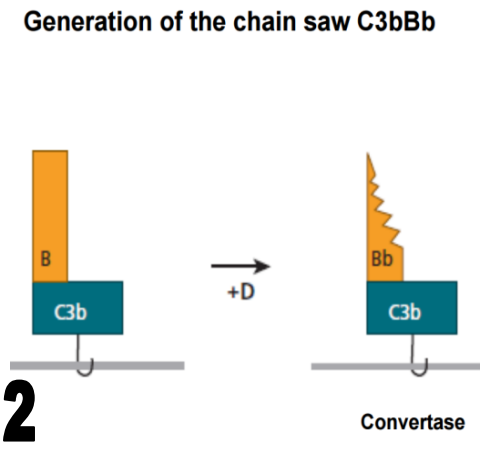
❖ Pathways of complement systems:

I) **classical Pathway** : it has a relation with the Antibodies "Abs"; so the attachment of Abs with antigens will cause the activation of this pathway. It'll recruit and activate some complements. "we'll talk about it in the next lecture"

II) **Alternative pathway**: C3 is the key molecule in this cascade.

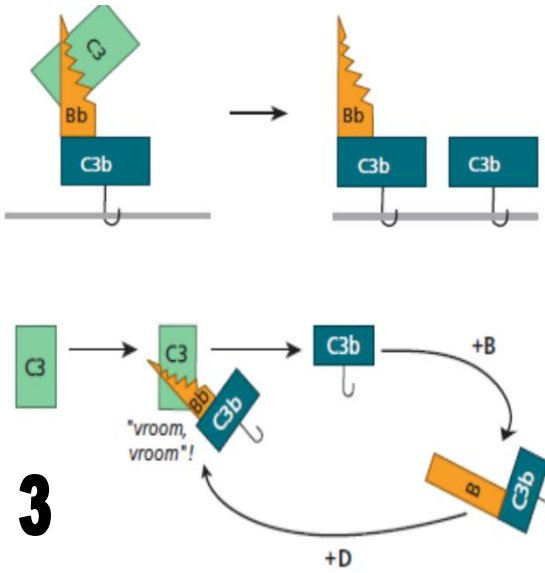


- C3 will have a spontaneous cleavageproducing C3a & C3b, C3b has 60 microseconds🕐 to either find NH2 OR Hydroxy group (OH) on the surface of the pathogen and attach to one of them in order to activate the alternative pathway.
  If neither were found, there'll be hydrolysis by a water molecule and neutralization for the C3b
  "و كأنّ شيئاً لم يحدث"😐 (figure 1)



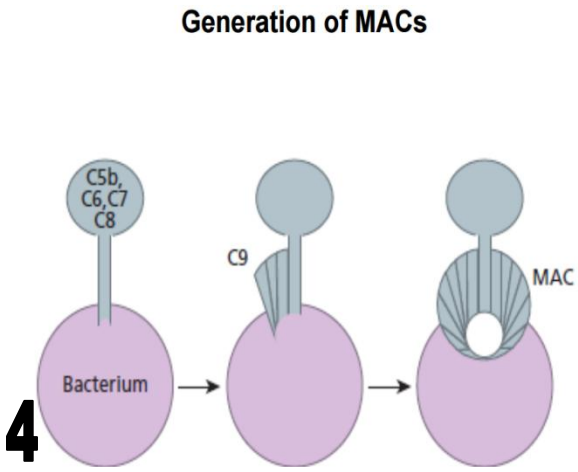
- C3b is also attached to some factors e.g. factor B , D or E etc.
  -Factor B will link to C3b which is already attached with the surface of a bacteria.
  -Factor D is responsible for the cleavage of Factor B
  -forming a **C3bBb** structure named **C3 convertase**
  "the base of the alternative pathway"
  imagine this structure as a saw , it's able to cut other proteins to activate the rest of the cascade (figure2)
  (note: Cytokines are not the same as Complement proteins)

- C3 convertase is responsible for the cleavage of more C3 molecules;
  (C3 starts the rxn by a spontaneous cleavage, which is not efficient to fight infections so we need to fasten those cleavages by C3 convertase)
  -convertase will come to the C3 molecule and cleaves it to C3a & C3b⟶ C3b will attach to the surface of bacteria *"now we have 2 C3b molecules, the one that was spontaneously produced and the one that's produced by C3 convertase"* factor B will attach to it and produce another C3 convertase and so on ...(figure 3)



- C3 convertase can cleave a C5 molecule to a C5a & C5b
  C5b will attach to the surface of a bacteria and form a structure that'll attach to other complement proteins (C6, C7, C8) and they form the stalk structure show on the surface of bacteria (figure 4).

  -whenever the structure (C5b+ C6+ C7+ C8) is completed , this will allow the attachment of C9 protein forming a ring around the bacteria, this will complete the structure and we'll name it **MAC** -membrane attack complex- this structure will work as a drill, forming a hole on the surface of bacteria and kill it ☠.



Summary: alternative pathway is a pathway where a group of complement protein will co-operate together to build a **mechanical structure** "MAC" on the surface of the pathogen; and so
DRILL 'EM AND KILL 'EM 🤗 (figure 4).

- Our cells contain NH2 &Hydroxy groups, but why they are not killed by the alternative pathway of the complementary system !??

  - because there are things on the surface of our cells that are able to reverse the action of our own complement proteins.

- The Three mechanisms that are able to protect our cells from the alternative pathway of complement system are :

1. human cells they process **surface enzymes** that <u>inactivate C3b</u> and produce "**iC3b**" inactive C3b ⟶ No MAC !!!
2. we have on the surface of our cells something called **Decay accelerating factor** "**DAF**"  or named as <u>*CD55*</u>, so incase C3b has attached to our cell surface successfully and produced C3 convertase "C3bBb", the DAF will stop this convertase and destroy it.
3. if neither of the previous steps work, and the MAC structure is about to be formed, then a protein called **protectin** or <u>*CD59*</u> are capable of kicking MAC away of the surface of the cell "before the attachment of C9".

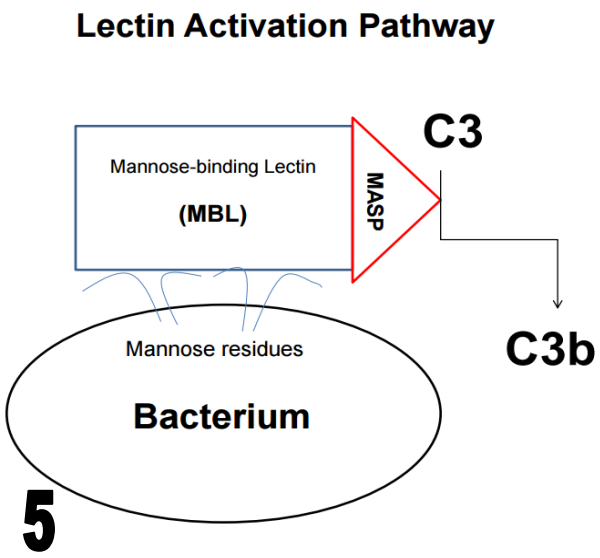
- Heart transplant is an example of the strength and importance of the complement system, once they tried to transplant a heart of a pig to a baboon , the result was ⟶ necrosis of the heart within minutes after the procedure , this was due to the innate immune system (because the molecules on the surface of the pig's heart that are responsible for the protection against the complement system weren't compatible with the complement system of the baboon, so the complement system of these primates "قرود" were able to attack the tissue of the heart).

III**) Lectin activation pathway**: it begins with a protein called Mannose-binding Lectin "**MBL**" *(mannose is a sugar found on the surface of a lot of microorganism cells except our cells, so it appearance will signifies the pathogen)*so MBL is able to identify the mannose residues and bind to them, MBL is attached to another protein called **MASP** "mannose-binding Lectin associated serine protease*(protease means: a protein that cleaves or cut other proteins)*" the structure (MBL+MASP) is able to cleave C3 to C3a & C3b then we'll repeat the same steps mentioned in the alternative pathway..... (figure 5)

we conclude that;

-Alternative pathway is a Random bombs 💣 "spontaneous cleavage of C3, then it randomly searches for an unprotected surface, binds to it, cascade goes on, or hydrolysis & neutralization will occur".

-Lectin activation pathway is a smart bombs 💻"MBL doesn't work until it finds a mannose residues, so this will guarantee toattack directly on the surface of the pathogen".



❖ Functions of the complement system:

1. **Building MACs**.
2. **Opsonization by iC3b** *(iC3b work instead of antibody, when the adaptive immune system is not activated yet)* A complement receptors on the surface of a macrophages will identify the iC3b and kill the pathogen.
3. **Chemotaxis** *"Chemotaxis means: the response of immune cell to a products formed in immune rxn"* (C3a, C5a act as anaphylatoxins, they form chemical gradient so that immune cell will identify it and migrate towards it).

Professional phagocytes

there are two types :

- Macrophages : are APCs "antigen presenting cells" found below almost all areas of the body e.g. skin, lungs, intestine, Liver.

- Neutrophils : are **NOT** APCs, they ingest and kill , short life.

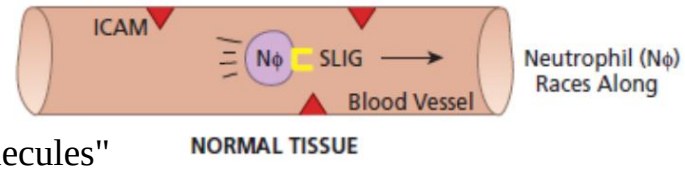
- macrophages exist in 3 states:
  I. **Resting state** "garbage collector" : they find dead tissue, cells ... ingest them and kill them → Low MHC II expression.
  II. **Primed state** :"good APC, good killer" the macrophage senses interferon gamma (IFN-γ) *"which is a very potent activator of macrophages"* → up regulate MHC II expression.
  III. **Hyperactivated state**: 2nd signal of danger → IFN-γ + LPS the macrophages will be highly phagocytic, more lysosomes, ROS, NO.

  "LPS= light poly saccharides , ROS= reactive oxygen species such as hydrogen peroxide, NO= nitric oxide"

  - if macrophages are overwhelmed, who come to the rescue?
    - **Neutrophils** , they are not APCs but rather **professional killers**.

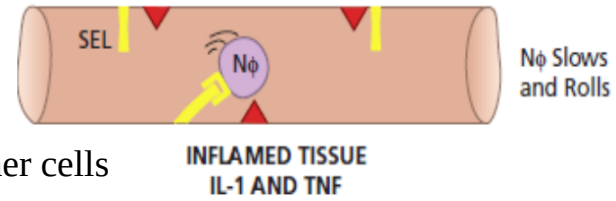
- how do Neutrophils know when and where to exit blood stream ?

- ✓ on the endothelial cells of a blood vessel we have something called **ICAM** "adhesion molecules"



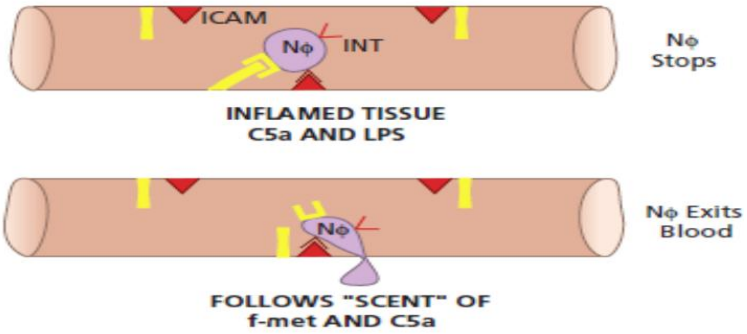
the Neutrophils contains **SLIG** receptor *"selectin Ligand"*, SLIG & ICAM doesn't match so the Neutrophil will keep on moving.

- ✓ suddenly we had an infection, this will cause producing of cytokines by macrophages and other cells such as interleukin 1 "**IL-1**"& Tumor necrosis factor "**TNF**".



after 6 hours of post tissue insult, with the help of these cytokines the endothelial cells will start expressing selectin "**SEL**" and will attach to the SLIG on the Neutrophil **only in the inflamed part of the affected vessel** , this attachment will cause <u>slowing down</u> of the Neutrophil.

- ✓ after slowing down the Neutrophil will be exposed to more inflammation product such as the chomotactic factor (C5a) this will cause the Neutrophil to produce Integrins "**INT**" which will attach to ICAM, the attachment of Neutrophil with selectin and ICAM <u>will stops it</u> , Finally it's time to leave the vessel,(the Neutrophil follows the SCENT of C5a & F-met *"is a peptide found in many bacteria".)* time to extravasate by squeezing itself through endothelial cells.

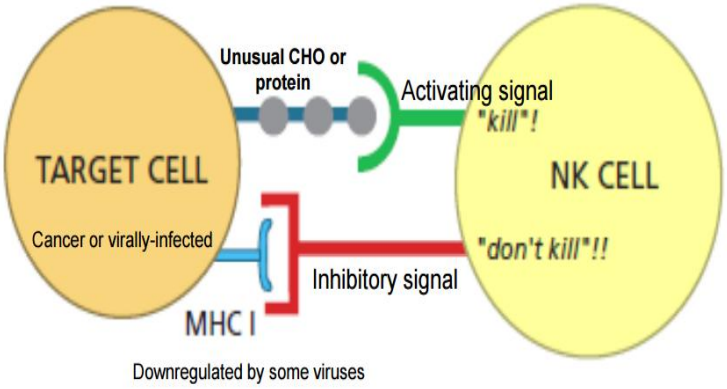


- ➢ Selectins & Integrins & their Ligands constitute a postal system for immune cell delivery, so that it will send the right cells to the right location to do the right job.

Natural Killer Cells "NK"

- Short-lived cells (1week), they have **NO** B or T cell **Receptor.**
- they are <u>ON CALL</u> "only when needed".
- mostly found in blood, liver and spleen (not in tissue, they are sent there when needed).
- Once they enter the tissue they will :
    1. produce cytokines (e.g**. INF-γ**) ⟶ Activation of macrophages.
    2. kill Cells by forcing them to commit suicide by injection of Granzymes or by "FasL-Fas interaction" ⟶ will induce Apoptosis.

- how do NK cells recognize their target ?
  -NK will search for Unusual proteins or carbohydrate, and then will attach to it, then will send an Activating signal saying "KILL".



  -on the other hand there are inhibitory receptors on the NK cell, so when they see MHC I "which is almost found in all of our cells" NK cell will think it's a normal cell after receiving an inhibitory signal saying "DON'T KILL".

  - some virally infected or cancerous cell, interfere with the MHC I expression, so the non presence of MHC I will send a signal to NK Cell saying "KILL".

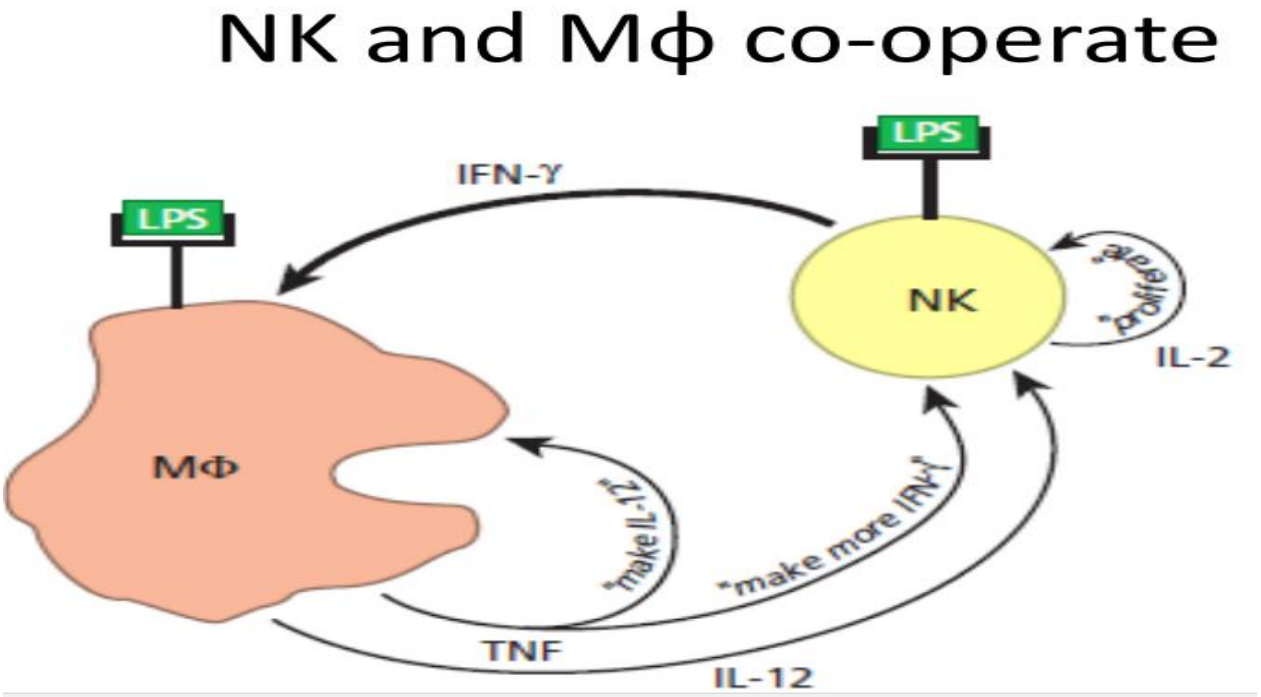
- NK cells become more active in the presence of some molecule such as LPS, type 1 interferons *"interferons α + β are very important in fighting viral infections".*

- NK cell combines both the actions of T-helper cells through the production of cytokines e.g. INF-γ with the actions of cytotoxic cells.

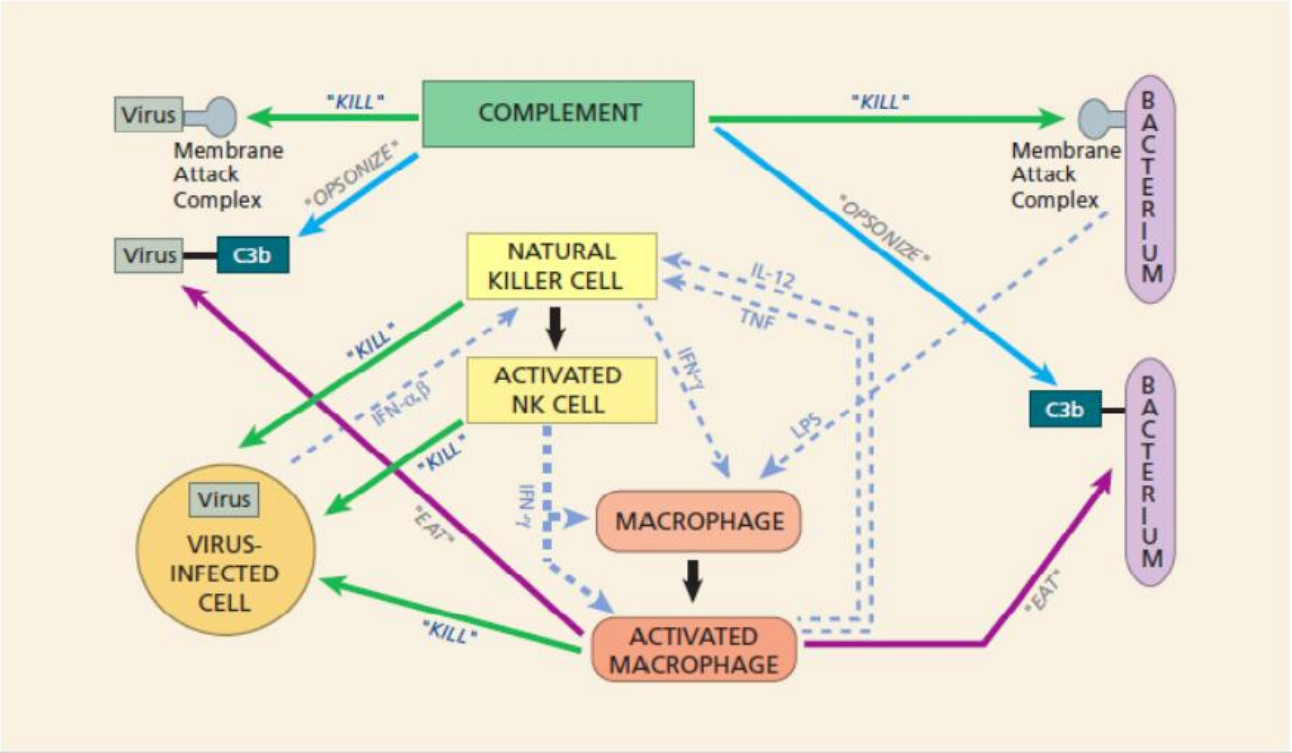
- **co-operation** between the NK cells and the macrophages:

  - ✓ NK cells will produce INF-γ which is a potent activator of macrophages.
  - ✓ once macrophages are activated they will produce IL-12 "a very strong proliferatory cytokine" and TNF , both of them are able to activate the NK cell.
  - ✓ normally NK secrete IL-2 "responsible for the proliferation of NK cell if there was a receptor for IL-2", in basal state there is no such a receptor.

- there is a Professional Phagocytes and complement co-operate.
  - ✓ Complement tags invaders and phagocytes eat them.
  - ✓ Activated Macrophages can produce complement components (C3, factors B and D) "C3bBb" and increase blood vessel permeability to recruit complement proteins from blood.



SUMMARY



A bacteria or a virus entered the body, the complement system will attach to their surface and form MAC which will "DRILL 'EM & KILL 'EM".
the complement system might do Opsonization by iC3b, which will attract the macrophages to attack the viral cell.
Natural killer cells "NK" are capable of :
- directly killing the viral cell
-or through Activated NK cells which can kill the viral cells directly
and at the same time secreting IFN-γ which will activate macrophages and produced Activated macrophage "tadaaaaaa :')" which will secrete IL-12 & TNF that will further activate NK cells or they will phagocytose opsonized bacteria or viral cells.
-Many viruses evolved defenses to protect them from the innate immune system.
• Innate system can help contain a viral infection in early stages, but more potent weapons are frequently required!

THE END❤