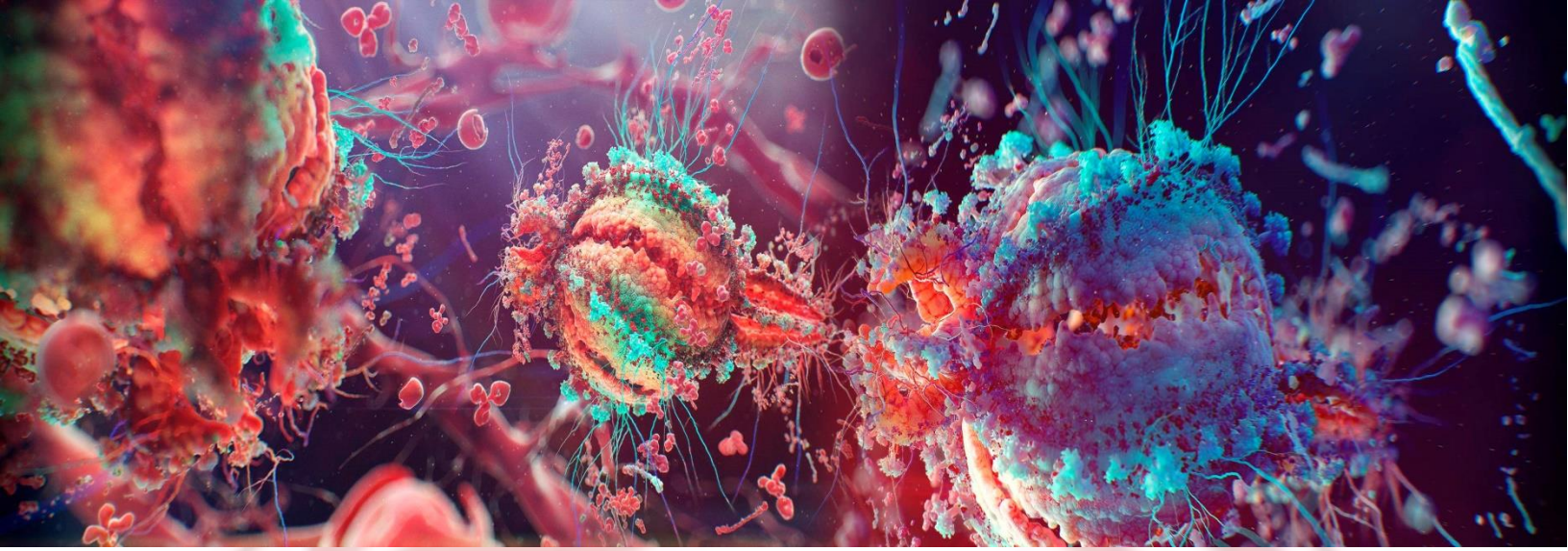

Immunology

Lecture (6)

Done by:
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Innate Immunity

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Objectives

- Discuss the concept of innate immunity - features, importance.
- Explain how the innate immune system recognizes foreign antigens in general.
- Outline the components of the innate immune system.
- Discuss how these components combat various foreign antigens.

Introduction

- protection against infections that relies on the mechanisms that exist before infection and are capable of rapid response to pathogens
(بكل بساطه زي الجلد ، الجلد بينولد مع الانسان)
- Innate immunity is the first line of defence against infection
- Characteristics:
  - set up at birth (يولد مع الشخص عند ولادته)
  - non –specific
  - hereditable
  - no immune memory
  - Little individual difference

Innate (Nonspecific) Immunity	
First line of defense	**Second line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Natural killer cells and phagocytic white blood cells • Inflammation • Fever • Antimicrobial substances

- We have talked about innate immunity before and we have mentioned that its the first line of defense and we have also said its : 1) non specific 2) rapid (مباشره او بعد ساعات)3)no memory 4) don't diverse from one person to another .
- رجع الدكتور قال انه هي عباره عن خط الدفاع الاول و برضو هي جزء من الاول و الثاني - first line of defense : skin , - second line of defense : phagocytosis (innate immunity is part of both first and second)
- First line of defense is the simplest line of defense .
- What is the difference between the first and second lines of defense ? That the second line is cellular and more complex

Innate Host Defense Mechanisms

- Physical factors
- Biochemical factors
- Microbiological factors
- Fever
- Innate Immune cells
- Cytokines
- Complement system
- Inflammation.

- the doctor only read this slide .

1. Physical Factors. Physical Factors : من اسمها بنعرف انها بتشمل (epithelium , skin , mucous membrane (

1. **Skin: microbes sloughed off along with skin cells, Microbes must penetrate several layers؟ كيف الجلد بيعمل دفاع**
   - **Stratified and cornified epithelium provides a mechanical barrier**
   - **Indigenous microbial flora competes with pathogens**

اغلب ال normal flora تولد مع الانسان و بضلها موجوده مكانها من غير ما تؤذينا ، لما تيجي بكتيريا و تعمل Infection ال normal flora بتعمل competitive rejection يعني بمعنى اخر ما بتخلي الميكروب ياخد مكانها ، زي كآنها بتمنعه من الارتباط بالانسان .

- **Acid pH inhibits growth of disease producing bacteria**

Ph of skin is acidic and as we know optimum ph for the bacteria to grow is the neutral ph, So skin help us to control bacteria and inhibit its growth .

- **Bactericidal long chain fatty acids in sebaceous gland secretions**

2. **Mucous Membranes: produce mucus to trap microbes, Most lined with cilia**

- Sebaceous glands secrete fatty acids , and fats acids are bactericidal (in another words it can kill the bacteria).

- 2) mucos membrane : we all know that the respiratory system is covered by mocous and cilia , also the gastrointestinal tract .
- As we know microbe can enter the body by 3 routes : 1) inhalation (respiratory) , 2) by gastrointestinal rout , 3)by blood (if he was injured)
- Okay so how does the mucos work ? By two steps : 1) trap 2) excretion

- تمام ، طيب لو اجى مريض و كان عنده cough and sputum ، هل من الصحيح اعطاءه anti cough ؟ هلا هاد ال cough بيحتوي على الميكروب فاذا انا وقفته من الخروج رح اكون زي كاني خليت البكتيريا و الفيروس جوا صح ؟ و هاد الاشي اكيد مو منيح لانه انا هيك بكون منعت الجسم يدافع عن حاله و يحاول يتخلص من الميكروبات ، فنحنا لما نفهم السعله من هاد المنظور بنفهم انه اعطاء ال anti cough لازم يكون بحرص جديد و مو على الطالعه و النازله .
- نفس هاد المبدا بطبقه على ال diarrhea and vomitting
- So simply you just have to think twice before giving an antiemetic or anidiarrhea and anticough drug , because we have to give the body the chance to defense itself .

2. Biochemical Factors

1. Low pH in vaginal and urinary tracts, and stomache
2. Defensins: short antimicrobial peptides, insert into bacterial membranes and form pores
3. Lysozyme: degrades peptidoglycan
   - Tears contain a high concentration of lysozyme (effective against gram positive microorganisms)
4. Interferon: are cytokines that trigger:
   - macrophage activation
   - production of substances to interfere with RNA viral reproduction

- Low PH ——> stomach have acidic PH , due to the presence of HCL , so any microorganism that will enter through food (gastrointestinal route of entry will be killed or inhibited by the stomach acidity)
- Almost all microorganisms are killed by the acidic PH but they have found out that H.pylori can resist the acidity .

- DEFENSINS : ، (من اسمها واضح انها بتعمل دفاع)

  هي عباره عي بيبتيدات صغيره ترتبط مع غشاء البكتيريا و بتخزقه .

  They are : 1) short 2) antimicrobial 3) peptides .

- Lysozyme : its degrades peptidoglycan , we should all know that peptidoglycan is part of the cell wall of GRAM+VE bacteria (may be found in gram-ve but more in gram+ve).
- SO , peptidoglycan is the main component of gram+ve cell wall .
- Lysozymes are found mainly is secretions such as tears , so tears. Will have the ability to destroy gram+ve bacteria(because conatins lysozyme

THE QUESTION IS :

- لو اجاك مريض عنده (cojunctivitis), اللي هو عباره عن التهاب بالعين ، (infection in the conjunctiva) هل رح اعطيه antibiotic لل gram+ve or gram-ve ؟

ANSWER :
We will give him an antibiotic for gram-ve , because tears in the eye which contain lysozyme will kill the gram+ve bacteria .

SO , tears have 2 roles : 1) washing machine for the eye .
2) contain lysozymes which kill gram+ve bacteria .

- Interferon : (there main function is in viral infections) , they are one of the cytokines types , its main function is to call macrophage in the viral infection and it helps the body to kill the virus .

- Cytokines are normally produced by the body , but know we started producing them artificially so we can fight viral infections as hepatitis .

Antimicrobial Peptides/Defensins

- Originally isolated from frog skin based on their ability to kill bacteria
- Small polypeptides (<10kDa) secreted at mucosal surfaces
- Four hundred peptides described to date
- Defensins (four families in eukaryotes)
  - α-defensins (neutrophils and intestinal Paneth cells)
  - β-defensins (epithelial cells)
  - Insect defensins
  - Plant defensins
- Defensins appear to act by binding to outer membrane of bacteria, resulting in increased membrane permeability
- May also play a role in inflammation and wound repair

Defensins:

- هدول اللي قبل شوي حكينا عنهم انهم ببتيدات ، بخزقوا البكتيريا .
- هلا كيف اكتشفوهم ؟ بنلاحظ انه الضفدع بعيش بالمناطق الرطبه و مع هيك ما عنده infection، مع انه القاعده بتحكي (كل ما زادت الرطوبه بتزيد الاحتماليه للinfection) ، يعني حتى نحنا بالعاده لما يجينا مريض عنده جرح بنحكيله يخلي الجرح جاف ، حتى ممكن مرات نمنعه من ال bathing ، لحتى ما يوصله ماء .
- طيب كيف الضفدع بالرغم من عيشه بمناطق رطبه ما عنده الinfection ؟ اكتشفوا انه بيكون عنده على جلده defensins .
- They are small polypeptides
- Have 4oo hundred type that have been classiefied into 4 groups (alpha , beta , insect , plant)
- We can notice that they are not only found in human but also in insects and plants .

- Defensins bind to the bacterial membrane —-> so it increases membrane permeability ——-> cell will enlarge until it lysis.
- Keep in mind that neutrophil and macrophages also have a role in wound repairing .

3. Microbiological Barriers

- Normal Flora: not part of immune system, but are part of first line of defense
- Protection they provide is considerable
  - Competitive exclusion of invading microbes
  - Produce compounds that are toxic to other bacteria
  - Stimulates immune system, providing a moderate amount of "exercise" to system, thereby enhancing it's function

Microbiological barriers / normal flora :

- Where do we find normal flora ? 1) skin (suchas staph aureus and staph epidermis 2) nose 3)oral cavity 4) hair .
- But we have to know that blood and organs are sterile . (sterile : means they are clean and don't have normal flora) , all organs and fluids inside the body (blood , liver ,CSF , kidney , heart , brain)
- حكى الدكتور انه ممكن يضحك علينا و يسآلنا شو نوع الفلورا بالكبد مثلا ، بس نحنا لازم نكون عارفين انه مافي هناك فلورا .
- Respiratory and gastrointestinal tract do have normal flora but the organs and fluids don't have normal flora .

- و زي ما حكينا قبل انه هي بتشتغل عن طريق :
- 1) complete exclusion (complete rejection) , discussed earlier .
- 2)produce compounds that are toxic to the bacteria .
- 3) stimulate the immune system
  بتحفز جهاز المناعه لحتى يتعرف على البكتيريا .
- Normal flora is generally a good thing so we don’t want to kill it .

4. Fever

- Mechanism of fever:
  1. Higher body temperature occurs as a result of certain cytokines called pyrogens
  2. Cytokines carried in bloodstream to hypothalamus
  3. Hypothalamus responds by raising temperature
- Fever inhibits growth of many pathogens by at least two mechanisms:
  1. Elevates temperature above optimum growth temperature
  2. Activates and speeds up a number of other body defenses

FEVER :

- There is no infection without a fever , we usually don’t like fever but its actually an immune and defensive mechanism .

- Hypothalamus : هو العضو الذي يحافظ على درجه حراره الجسم مهما كانت الظروف الخارجيه سواء كانت ثلج او شوب او ربيع بحافظ على درجه حراره الجسم لتكون ٣٧°

- هلا في حال صار عنا التهاب الجسم رح يفرز نوع من ال , cytokines ، بنسميهم pyrogenes بيروحوا على الhypothalamus ، و بيعطوا امر انه يرفع درجه حراره الجسم كآحد خطوط الدفاع لانه الحراره العاليه بتمنع نمو الميكروبات .

- Fever act as a defense mechanism by 2 steps : 1)elevate temperature above the Optimum growth temperature so it inhibits microorganism growth . , 2)activate and speed up number of body defense mechanism as :1) neutrophil and macrophage .
- Optimum temperature for microorganism to grow is = 37 .

- Do we decrease temperature all at once ? No , because its one of the defense mechanisms, so we decrease it slowly .
- لنحكي اجاك طفل درجح حرارته ٤٠ هل بعطيه خافض للحراره ؟ نعم اكيد بالرغم انه الحراره هي احد خطوط الدفاع الا انه الها اثار سلبيه كتيره و بتعمل Damage of the brain cell

- The doctor said that meningitis has nothing to do with the fever . And this has been misunderstood by many doctors , as meningitis is caused by the transfer of microorganism into brain cell not due to fever .

- QUESTION : what type of microorganisms dies at temperature of 40 ? Answer : malaria (a parasite)

على درجه حراره ٤٠ كلهم بموتوا و لما تقل درجه الحراره بترجع الملاريابتتكاثر من اول و جديد

5. Innate Immune Cells

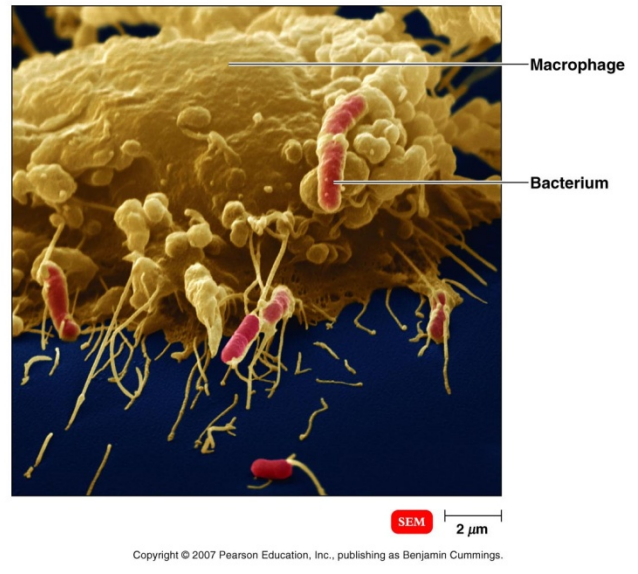
(all immune cells except for lymphocyte)

Cell type	Pricipal function(s)
Monocytes/Macrophages	Phagocytosis, inflammation, T-cell activation, tissue repair
Neutrophils	Phagocytosis, inflammation
NK cells	Killing of infected or tumor cells
Dendritic cells	Phagocytosis, activation of naive T-cells
Mast cells	Inflammation
Eosinophils	Defense against parasites

- The first cell called in inflammation is the neutrophil .
- Non steroidal anti-inflammatory drugs are the most prescribed drugs such as : voltaren and ibuprofin .
- Inflammation can be a defensive mechanism and its can positive or negative mechanism .
- If it was under control and in the right place then its a positive mechanism , but if it went out of control and started effecting healthy and normal cells then its a negative mechanism
- Natural killer cell works on viral infections and tumor cell . (we took its cytotoxic effect before)

Phagocytes

- Performed by Neutrophils and Macrophages
  1. Phagocytosis is the capture and digestion of foreign particles
  2. Chemokines are cytokines that attract macrophages and neutrophils to infected tissues
  3. Opsonins attach to microbes to increase the ability of phagocytes to adhere (opsonization)



Phagocyte :
(الدكتور قرا السلايد)

- Chemokines are another type of cytokines which attract macrophage and neutrophil to the site of infection and to the lymph node . And vice versa (it can also kick them outside the infected cell)
- SO , keep in mind the types of cytokines we took until now : a) interferons (that used to deal with viral infection) b)pyrogens (go to hypothalamus to increase body temperature) c)chemokines :cytokines that attract macrophage to the site of infection .
-

What is the difference between phagocytosis and opsonization ?

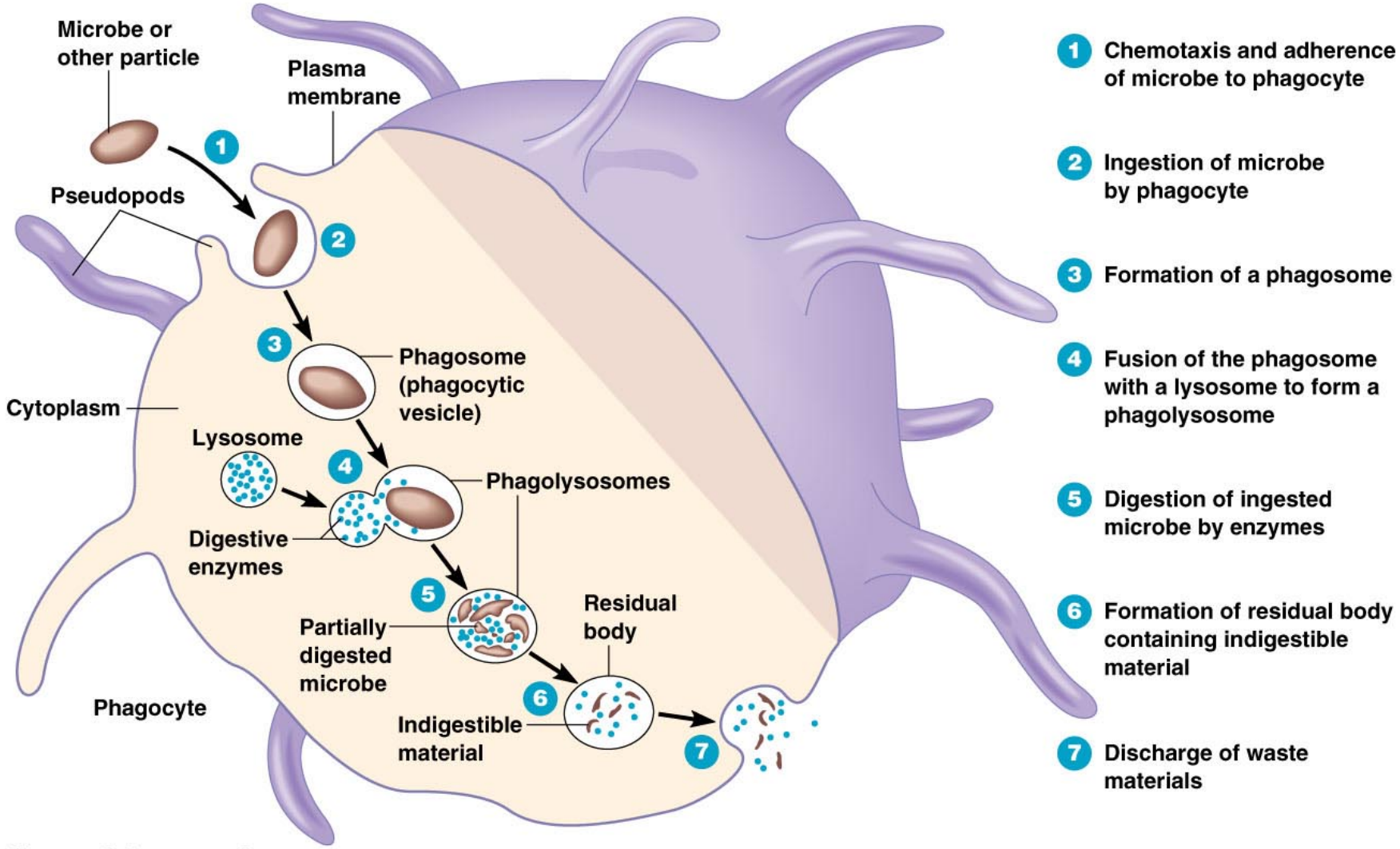
- If an antibody coat the microorganism and then it call macrophage then this mechanism is called opsonization

يعني بمعنى لخر لو الميكروب دخل جوا الmacrophage من غير الحاجه لantibody، هاي بنسميها phagoctosis ،
لاkه مرات ال macrophage بتتعرف عى الميكروب لحالها ، بس مرات رح نحتاج ال ANTIBODY لحتى يعمل
labelling للميكروب و هيك بصير اسمها opsonization

Steps of Phagocytosis

- Recognition
- Ingestion- pseudopods engulf microbe through endocytosis
- Vacuole Formation- vacuole contains microbe
- Digestion- vacuole merges with enzymes to destroy microbes
- Exocytosis- microbial debris is released

The doctor Read the slide and said that its better explained on the drawing in the next slide .



Phases of phagocytosis

١) اول اشي بده يصر عنا uptake —-> يعني بده يدخل الميكروب على ال phagocyte.
٢)بعدين بصير عنا vacuole formation ، بتعمل احاطه للميكروب (vacuole coats the microorganism)
٣)بعدين بصير عناlysis ، عن طريق الlysosomes and digestive enzymes
لاحظوا كيف ال phagocyte راحت نادت digestive enzymes ، و دخلتهم لجوا ال vacuole
٤)ال digestive enzymes and lysosomes رح يحطموا البكتيريا
٥)لما تتكسر علو الاخر بصير اسمها residual bodies
٦)بصيرلها اخراج لبرا ال phagocyte

****ليه احطنا الميكروب ب vacuole؟

لحتى لما يصيرلها digestion ما تؤذي الانسجه السليمه ، كمان لحتى نخفف من ال infection .

#microorganisms that resist phagocytosis :
1) TB (bacteria), Leshmenia (parasite), salmonella (bacteria) , HIV (virus)
** resist means that they enter the phagocyte but they multiplicate inside it) (they are literally multiplying inside your immune system and that is really bad .

#encapsulated bacteria they can't be phagocytosed (they don't enter the macrophage)
macrophage usually don't recognize virus due to its small size , so there is something called interferons that helps phagocyte to recognize the virus .

Innate Immune Recognition

- All multi-cellular organisms are able to recognize and eliminate pathogens
- Despite their extreme heterogeneity, pathogens share highly conserved molecules, called “pathogen-associated molecular patterns” (PAMPs)
- Host cells do not share PAMPs with pathogens
- PAMPs are recognized by innate immune recognition receptors called pattern-recognition molecules/receptors (PRMs/PRRs)

We have said that innate immunity is non specific right .. so it will deal with all microorganisms .. okay so how does it recognize the microorganism ? (بمعنى اخر كيف بتعرف انه هاد جسم غريب مو خليه من جسمنا)

عن طريق اي اسمه PAMPS .... يعني لنفهم الفكره خلينا نفكر بالانسان هلا كل الاشخاص عندهم عيون و هاي احد الطرق لتميز الانسان تمام ، بس لون و شكل العيون بيفرق من شخص لاخر و هاد لاشي بنحكيله pattern

و هاي هي فكره ال pamps هي عباره عن اشياء موجوده عند كل الميكروبات لحتى يقدر الجسم يتعرف عليها بس تركيبتها بتفرق من ميكروب لميكروب على سبيل المثال: lipid A in gram-ve bacteria and peptidoglycan in gram+ve bacteria , viral RNA which is completely different than human RNA .

***The PAMPS are not found in the human body , for sure because if they were found in human body then the immune system will start to effect the normal tissue and then we will have autoimmune diseases

Typical PAMPs

- Typical PAMPs:
  - Lipopolysaccharides
  - Peptidoglycans
  - Certain nucleotide sequences unique to bacteria
  - Other bacterial components
- Binding of Innate immune receptors and PAMPs:
  - Mediate inflammatory cytokines
  - Antigen-presenting cells recognize PAMPs

6. Cytokines

- In response to microbes, macrophage and other cells secrets proteins called cytokines that mediate many cellular reaction in innate immunity
- Cytokines act as
  - Inflammatory mediators
  - Communication between leukocytes and leukocytes and other cells
- 4 kinds:
  - Chemokines: important in chemotaxis of immune cells
  - Interferons: glycoproteins important in the control of viral infections; also help regulate cells involved in immune response
  - Interleukins: important in innate immunity, inflammation, and adaptive immunity
  - Tumor necrosis factors: help kill tumor cells, initiate programmed cell death (apoptosis)

CYTOKINES :

- Proteins that have a role in innate immunity (we also have cytokines that play a role in adaptive immunity)

- Cytokines have two functions :1) inflammation 2) communication between leukocytes and other cells .
- 1) chemokine
- 2) interferons (we mentioned its function in viral infection)
- 3) interleukin (have a role in inflammation)
- 4)TNF (tumor necrotic factor) : acts on the tumor cell
- 5) pyrogens : goes to hypothalamus and increase body temperature
- There are many other examples that we will mention later on .

6. Complement System

- The complement system is a collection of circulating and membrane associated proteins that are important in defense against microbes
- Many complement proteins are photolytic enzymes and complement activation involve the sequential activation of these enzymes called the enzymatic cascade
- Three pathways to activate the complement system
  - Classical: activated by antibody binding to microbes or antigen (adaptive part)
  - Alternative: directly activated by microbes (innate immunity)
  - Lectin pathway (binding to mannose-containing carbohydrates) (innate immunity- no need for antibodies)

Complement system :(CS)

- Its a part if innate immunity that is activated by antibodies and it causes lysis of cell .

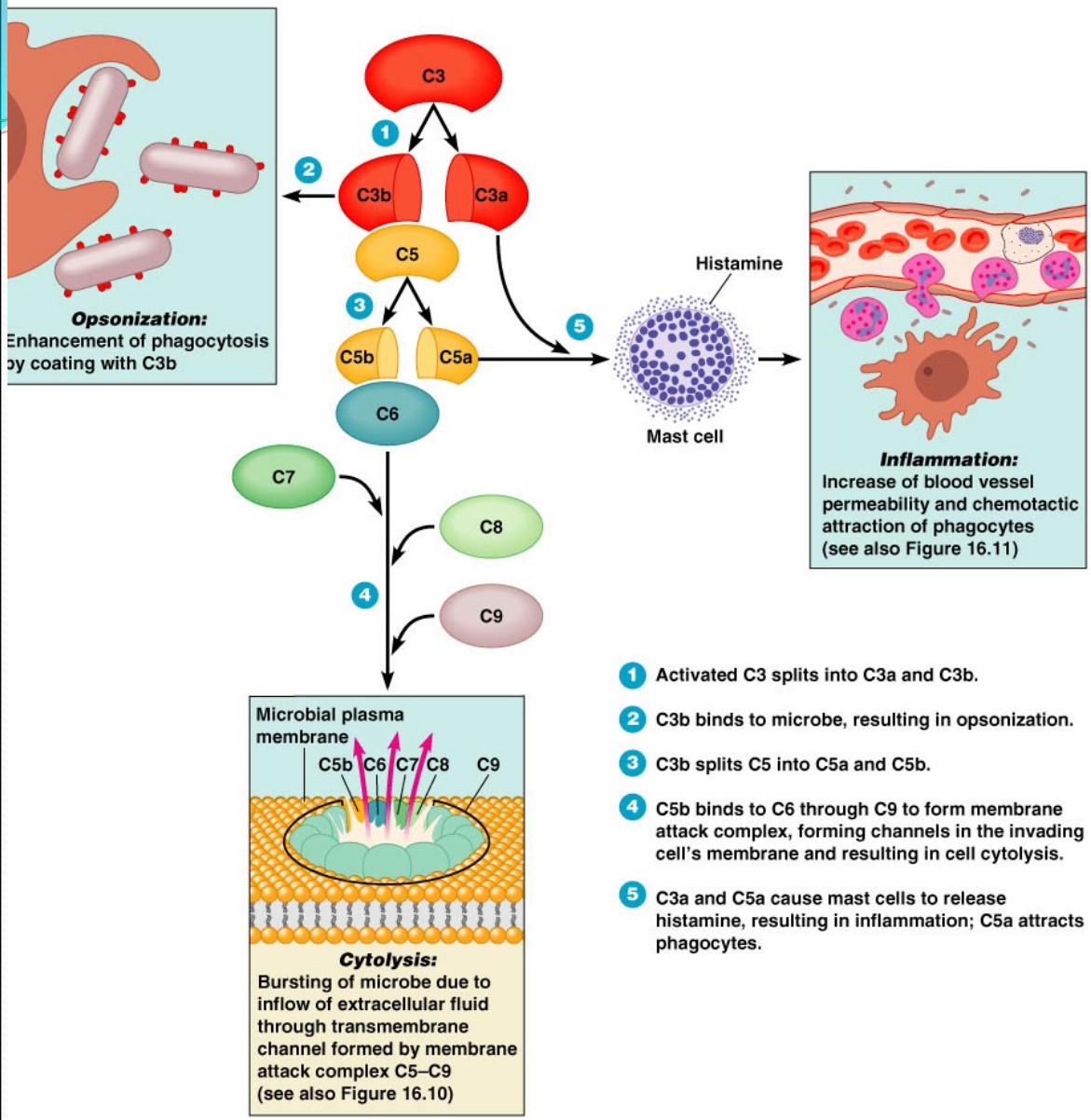
همه عباره عن مجموعه من البروتينات ، اول واحد بال CS هو عباره عن C1 و بضل ماشي ليوصل C9 (هلا نو شرط دايما نبدا منC1 في بعض الحالات ممكن نختصر الطريق و نبدا من C3 ،

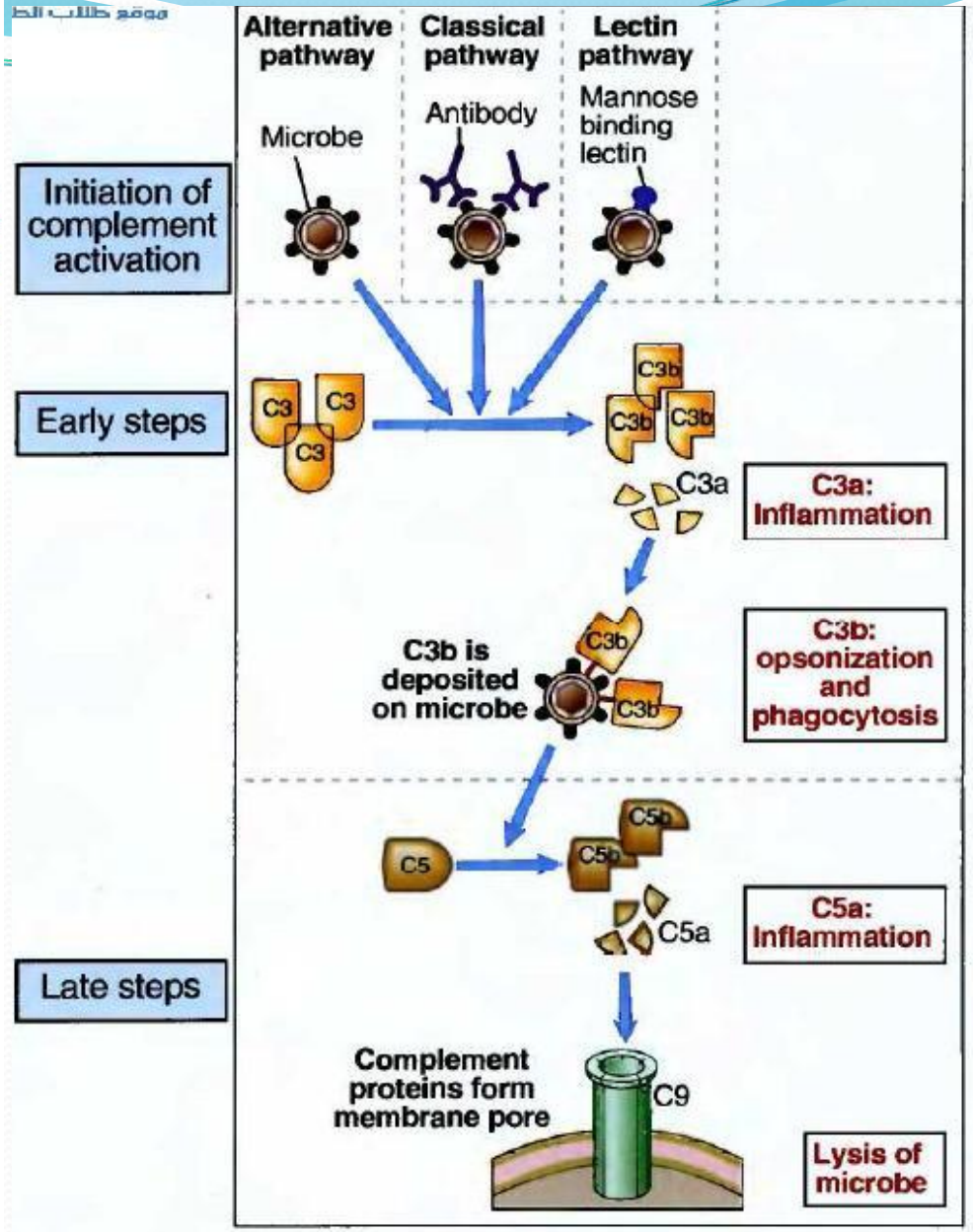
*** هل المفروض الCS يحطم الخلايا الجسم ؟ طبعا لا ، الا اذا كان عليهمAntibodies .

- C1-C9 are found in the body in the inactive form , C1 ia activated by AB , but then they start activating each other (the antibody activate C1 , then C1 activates C2 , then C2 activates C3 , ….. until we activate C9 .

- If the microbe activated C1 without an antibody then its called alternative (innate part) (microbe * C1)(C1 activates C2—->C9)
- If it was activated by an Antibody then its classical (adaptive part) (microbe * antibody *C1) (C1 activates C2 —-> C9)
- CS has two types : 1) first type is free 2) second type are membrane bound

- Host cells have complement regulatory proteins on their surface that protect them from spontaneous activation of C3 molecules while microbes can activate the complement pathway but it have no regulatory proteins
- When pathogen activates the complement system this initiates innate immunity response by three main mechanisms:
  - Inflammation
  - Phagocytosis and lysis
  - Opsonization





Role of innate immunity in stimulation of adaptive immune response

- Adaptive immune system activation (T or B-cells) need two signals for activation
  - First signal: antigen recognition
  - Second signal: derived by innate immunity

- The end of the first exam .
- If you have any questions don’t hesitate to ask and please if you have any notes let me know .
- Best of luck .

* شرح سيستم الـ complement System

* زي ما حكينا الـ complement System هو عبارة عن مجموعة من البروتينات البروتينات تؤدي في النهاية lysis of bacterial cell

* كلهم من C1 لـ C9 وزي ما ذكرنا قبل انه في شرط دائماً يبدأ من C1 ممكن نختصر الطريق ويبدأ من C3

** we said that we have 3 pathways:-

1) Alternative (innate) → when Ag directly binds to C1.

2) classical (adaptive) → when Ag bind to Ab, and then Ag*Ab complex bind to the C1. to activate the complement System.

3) lectin pathway, also innate & no need for Ab as an intermediate. (mannose containing Carbohydrate)

C3 → C3a + C3b

C3b is an inflammatory Mediator, we find it high in inflammatory disease

C3a is Responsable for opsonization

C5 → C5b + C5a

C5b

↓

C6

↓

C7

↓

C8

↓

C9

* C5b activates C6 → (7 → C8) → C9

and then activation of C9 causes cytolysis.

- you should know that C3a, C5a, have a Role in inflammation, in addition C5a has a Role in phagocytosis.

*: Summary:

1) Activated C3 by C2, will split into C3a, and C3b, (C3a has a role in inflammatory Reaction)

2) C3b binds to microbe, resulting in opsonization

3) C3b splits C5 into C5a, C5b (C5a has a role in inflammation)

4) C5b binds to C6, and when C9 is activated, it will form membrane attack complex, forming channels invading cell membrane resulting in cell lysis. (cell cytolysis)

5) C3a, C5a, causes mast cell to Release histamine, resulting in an inflammation, C5a attracts phagocyte.

* C3a: inflammation
* C5a: inflammation
* C3b: opsonization & phagocytosis
* C9, cytolysis