  
  
***Title of Lecture: inflammation***

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***Sheet no: 7***

***Refer to slide no. :46-73   
  
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- Each step in the inflammation includes changes that occur in the tissue in order to build up the inflammatory process   
  
- 2 main parts in the inflammation response :  
1- vascular changes   
2-cellular changes . that includes infiltration of the tissue by different types of inflammatory cells   
  
very important differentiating point is the cells that infiltrate the tissue , & this is depended on chemo taxis agent and that’s why the chemo taxis is important part of inflammation and that’s why we havre different types of cells that although groups of infectious agent ,for Ex: bacteria produce neutrophils ( neutrophilic infiletrate ) while parasite produce other type

* - type of the inflammatory cells can give us cue about infectious agent although do Not give us a specific type of bacteria or a specific virus , however type of cells that infiltrate the tissue can give us a cue either its a bacterial or a viral or fungal infection   
    
  cells infiltrated or concentrated at site of inflammation due to chemotactic agent , these agents are chemical medatiors that attract a specific type of cells and this is what we called chemo taxis  
     
    
  chemo taxis (( attraction certain type of cells )) can due to the presence of bacterial products   
  - in general , most of bacteria they are chemotactic for Neutrophils , that is why neutrophilic Infiltrate of any tissue is an indicative for inflammation  
    
  - certain cytokines or chemokines ,they are produced at the site of inflammation ,they have a selective action on the cells . chemotactic agents for of neutrophil attraction and others for eosinophil ,,so they are different   
    
  - chemical mediators that important in the inflammation are many types ,one of them is a complement proteins ,which usually( Normally ) exist in the blood , they are responsible for aprocess of coagulation . however certain component of this complement system is **C5a** which activated once they are degraded into 2 components ( A and B ) , each one A & B has its own action . C5a it’s a chemotactic agent which is important for inflammation process   
    
   - leukotrienes , substances that produced by action of 2 different enzymes , (( there is 2 pathways depending which enzyme is involved )) :   
    
  - lipooxygenase pathway ,which acts on **arachidoinc acid (AA)** , which asubstance exists in the cell produce leukotrienes , the most important leukotrienes is **B4** which acts as chemotactic agent   
    
    
  - depending on the which type of the chemo agent infiltration of tissue occurs . these chemoagents are produced in the tissue in response to the presence of infection, or tissue damaged ( dead cells ) ,or immunologic interaction  
    
  - Regardless what starts immunologic interaction ( infection or, anti-gene anti-body complex which result due to alteration , this alteration maybe leads to cross infection between antibody toward anti gene itself , or unknown reason )   
    
  - in order to affect any cell we have to produce signals ,&these signals are proteins , enzymes ,hormones   
  - these signals that come from outside should affect nucleus in order to affect the cell , so simply all these signals should bind with receptors on cell surface  
    
  - after binding there is some changes within the receptors structure to activate enzymes inside in the cell and this is associated with transduction , in order to transmit the signals from outside to inside   
  - so these signals should transmitted to the cytoplasm and in the nucleus these signals leads to :   
  activation of proteins , enzyme production , structural changes in proteins present in surface , increase affinity , expression ,,,,etc   
  all these results are the end result of signalling..  
    
    
  types of inflammatory cells depends on different things : -   
  1- the age of inflammatory response :   
  age ↓→ neutrophil ↑  
  age ↑→ chronic inflammatory cells ( plasma cells , lymphocyte cells ) ↑  
     
  this is happen for many reasons we will talk about them later   
    
  2- type of stimulus :   
  duration is not always important because some stimuli even from few start of inflammation there is amonocyte and lymphocyte cells not neutrophil ,why ? because the type of stimulus is different , for ex tuberculosis is a bacteria ,still its response not by neutrophil , its by chronic inflammatory cells ,that’s why its causes by a specific type of inflammation   
    
  Neutrophils is the predominant cells in first 6-24 hours in bacterial infection and then they start to be less and replaced by monocytes , so they are need to kill the bacteria how ever then this dead bacteria and damaged tissue should be removed so the tissue start to be infiltrated by monocyte in order to carry out phagocytosis and elimination   
    
  why neutrophils ?   
  1- more numerous than other cells   
  2-they are sensitive to chemo tactic agent that’s why they respond very early in the inflammation process   
    
  3-they can adhere ( bind ) to adhesion molecules than others  
    
  so , their number , sensitivity , activity are higher than others so they respond quickly to the signals   
    
  neutrophils , however they shot lived ( 24-28 hours ) and that’s why first group on Neutrophil in the tissue is replaced by another within 24-28 hours   
    
     
  exceptions how ever they are   
  1- pseudomonas infection : there is continuous signalling for neutrophils that’s why the neutrophilic respond is very huge ( more time, more amount )   
    
    
  2-viral infection : from the start the predominant cells is lymphocyte , because viruses associated with chemotactic agents toward lymphocyte , so whe their number is huge we say there is a viral infection   
    
  3- parasitic infection or hypersensitivity reaction are associated with chemotactic agents toward eosinophils   
    
  inflammation can not b achieved without activation of leukocytes because they are important since they secret mediators that are needed in inflammation and also they participate in phagocytosis   
    
   **Stimuli for activation include: microbes , necrotic cells , mediators**   
  leukocytes respond to these microbes through receptors on cell surface . there are many receptors but the 2 most 2 important receptors are
* 1- Toll-like receptors---endotoxins (LPS)
* 2- 7-transmembrane G-protein-coupled receptors---certain bacterial peptides & mediators  
    
  - why they are important , because there is some diseases related to their absence or deficiency ,so the response of bacteria will be less and will we not have a proper inflammation process ,that’s why microorganism live for more time and leads for more destruction   
    
    
  **phagocytosis**   
    
  - it’s a very important process In the inflammation because without it microorganisms can not be eliminated , however after phagocytosis microorganism should be killed within phagosomes inside the cytoplasm of macrophages , because phagosmes fuse with lysosomes that contain many types of enzymes   
    
  - these enzymes act on microorganism ,they produce killing of microorganisms and in addition to other system process which system associated with production of free radicals , changing of pH why ?   
  because not only action of enzymes can kill microbes sp cells have different pathways ( lysosomes , free radicals , chemical mediators,, etc ) inside the phagosome to ensure that they are killed (( additive process ))   
    
  # 56 slide -  
  different agents act on cells . and each one has its own receptors in order to affect the cell   
    
    
    
   **opsinization :** \*  
  In order to enhance the phagocytosis process we can make them more recognizable and eatable by macrophages by covering or coating microorganisms by proteins called **: opsonins**this will enhance the efficiency of phagocytosis   
    
     
    
  The most important opsonins are:  
   1- Antibodies esp. IgG
* Complement protein C3b 2-
* 3 - Collectins: Plasma carbohydrate-binding lectins which bind to M.O cell wall sugar groups  
    
  Importance of opsinization : -  
  1- Enhancement of engulfment
* 2- Cellular activation that enhance degradation of
* ingested microbes  
    
  steps : .-

Engulfment →extension of pseudopods →phagocytic vacuole → fusion with lysosome →phagolysosome → discharge of lysosomal granules

1. - There is 2 enzymes important in killing in the cytoplasm :   
     
   **1- reactive oxygen molecules** : they be part of many things in the cell inflammation , aging..etc . they are deficient electrons molecules so they are unstable , and in order to get their stability they react with the sites which reach of electrons like proteins and nucleic acids   
     
    **2-lysosomal enzymes** : they are many types   
   Oxidase- A  
   B- Myeloperoxidase

elastase -C  
 hydrolase- E

- they react with microorganisms and cell itself that’s why they produce destruction   
  
- in addition to reactive oxygen molecules and lysosomal enzymes which represent the first line for killing we have agents once they bind to the cell surface of bacteria the permeability increases , which means the death of bateria   
like major basic proteins in eosinophil and defensins …(slide66)  
  
  
  
  
slide 67  
inflammation will produce some diseases   
**1-acute diseases**   
A- Acute respiratory distress syndrome (Neutrophils)  
destruction of alveloi which affects gas exchange which leads to respiratory failure   
  
- - Acute transplant rejection (Lymphocytes, Abs & complement.)b   
transplanted organs can be rejected because the have foreign antigens , which recognized by antibodies ..anti gene-antibody complex leads to inflammation eventually the transplanted organ will destructed   
(( that’s why we give patients who have a transplanted organ immune suppression))  
  
C- Asthma (eosinophils, IgE) …hypersensitivity reaction and whole process is an inflammatory   
  
D- Glomerulonephritis (Ab, complement) … groups of diseases affect the kidney , most of them anti gene-antibody complex , either antibody formed in the blood or direct on the kidney 'localy formation of antibody '  
  
E- Septic shock ( cytokines)  
  
F - Vasculitis (Ab, complement, Neutrophils)

**2- Chronic diseases :**

1-Arthritis (lymphocytes, macrophages, Ab)  
chronic inflammation of joints

2-Asthma ( eosinophils, other WBC, IgE)…it culd be chronic or acute

3-Atherosclerosis (Macrophage, lymphocytes)… its not oly deposition of fatty material its an inflammatory response to this material that’s why destruction of vessels occurs

4-Chronic transplant rejection (Lymphocyte cytokines)…. it could be acute or chronic

5-Pulmonary fibrosis (Macrophages, Fibroblasts)….very serious diseas which end up with fibrosis lung which can not be functional as normal ' inflammatory response '  
  
  
 \* every part /step in the inflammation process can be defective :

* 1- **bone marrow suppression** caused by tumors and chemotherapy or radiation (resulting in decreased leukocyte numbers) mechanism of defense of leukocytes dosent exist that’s why patients in hospital are separated

**2-metabolic diseases** such as diabetes, anaemia (causing abnormal leukocyte functions) suffer from repeated infection patients   
  
  
  
**inhearted defects in leukocytes \*\*\***

1. Defects in leukocyte adhesion

a. LAD type 1( defective integrins LFA-1 and Mac-1 )

b. LAD type 2 (absence of sialyl-Lewis X )   
  
both types 1 & 2 suffer from frequent recurrent sever infection-   
 ,

2. Defects in microbicidal activity

e.g chronic granulamatous disease : very famous disease in children , they deficiency in oxidase enzyme which important in Regeneration of Free Radicals   
patients , after engulfment of microorganism they can kill them because there is no free radicals that’s creat collections of activated macrophages that cant eliminate microorganisms   
  
  
3. Defects in phagolysosome formation   
defect in phagocytosis , macrophages cant engulf microorganisms

e.g Chediak-Higashi disease : auto recessive immune deficiency disorder , they suffer from frequent infections

4. Defects in Toll-like receptor signaling pathway :  
they don’t sense of bacteria , so there is no inflammatory response