



PATHOLOGY

Sheet no. 6



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CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

All cells collaborate to achieve the desired inflammatory response.

- **Macrophages**
- **Lymphocytes + plasma cells**
- **Eosinophils**
- **Mast cells + basophils** (sometimes)

Now let's talk about each one of them:

MACROPHAGES

- **Origin:** circulating monocytes (It's called Monocyte_Macrophages system), sometimes they add dendritic cells to them.
- **Secretion:** many mediators, most important are cytokines (TNF, IL-1) and chemokines.
- Feedback loop with T cells, **collaboration** between them.

Example: macrophages process and present antigen via MHC II to T-helper cells.

- **Phagocytosis:** two major cells: macrophages and neutrophil(PMNs)
- **Half-life:** Circulating monocytes 1-2 days, if they are NOT activated and recruited to tissue. Once they go to tissue (migration, rolling, adhesion, transmigration) and be activated they live for long time (for ex. month).
- **Tissue Macs:** Kupfer cells (liver Macs), sinus histiocytes (lymph nodes and spleen), alveolar Macs, microglia(CNS- brain).
- Mononuclear
- **Activation of Macs:** two methods:
 1. **M1** classic pathway, pro-inflammatory, most of them secrete mediators that enlarge and entice inflammation
 2. **M2** alternative pathway, participate in initiation of R4 (regulation of inflammation).

1-Bone marrow gives Hemopoietic stem cells that differentiate to macrophages.

2-progenitor in yolk sac and fetal liver, are the origin of Macs that circulate then go the tissue (kupffer, alveolar, microglia...)

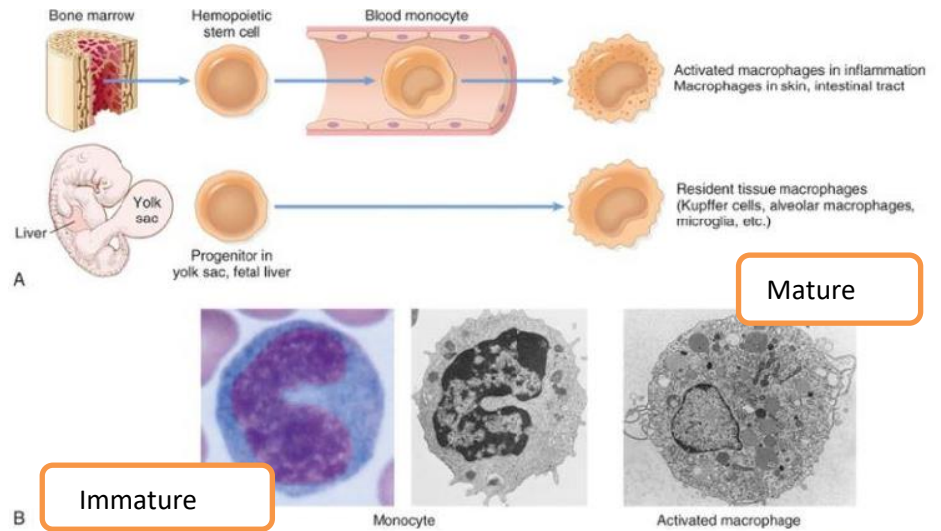


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t...

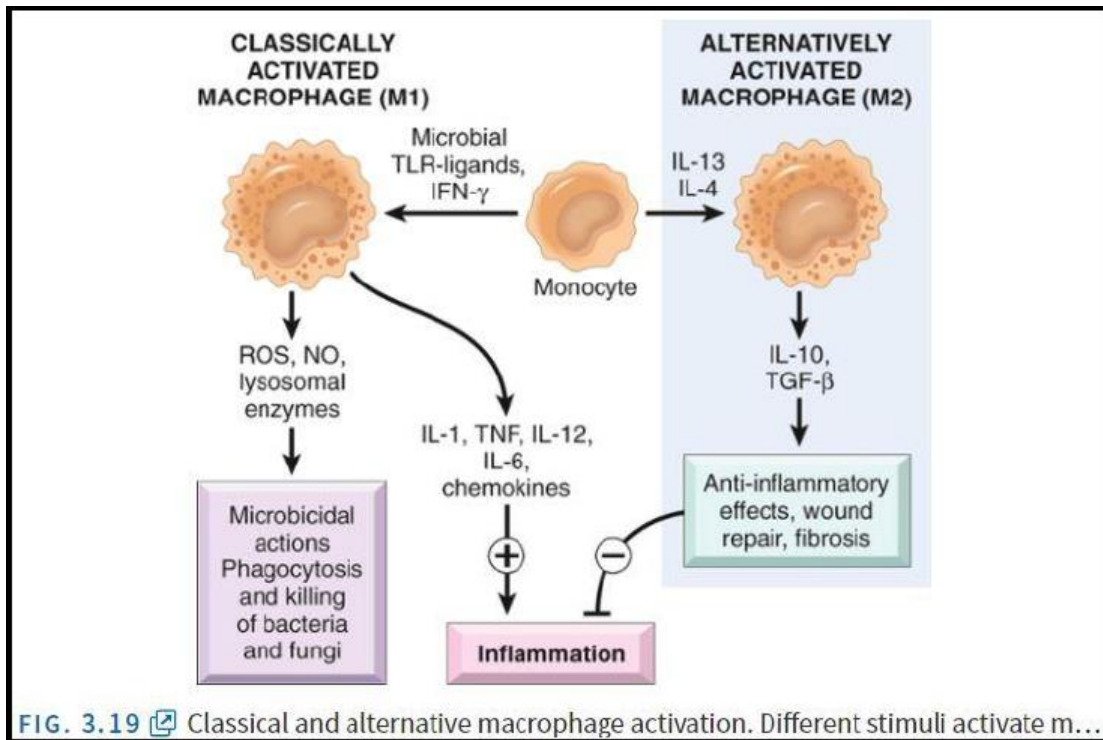
IN GENERAL:

- The mother cell: small in size, big nucleus (nuclear cytoplasmic ratio is high).

So when we take a peripheral smear (مسحة من المحيط) looking for Leukemia for example, we look for blasts immature cells that have large bean shape nucleus.

- The mature cell: (when the cell get into circulation)cell enlarges, nucleus get smaller, kidney shape, more abundant and functional cytoplasm, still can't see granules but they have more cytoplasmic organelles.

Note: granules same as lysosomes, but granules can be seen easier. Macs granules are less than PMNs'.



Activation of macrophages:

Classic M1 pathway:

- Microbial, bacterial, virus - TLR ligands - IFN- γ , stimulate the activation of monocytes to M1 classic pathway.

Remember: IFN- γ is secreted by T cells and NK cells.

- Pro-inflammatory
- Phagocytosis, killing
- Secrete cytokines, ROS, NO, lysosomal enzymes
- R3 (removing) stage

Alternative M2 pathway:

- IL-13, IL-4 (interleukins) activate Macs in M2 pathway
- Secretion : IL-10, TGF- β (transfer growth factor, the major player in repair)
- Anti-inflammatory effects (R4), and stimulation for repair wounds and fibrosis (R5).

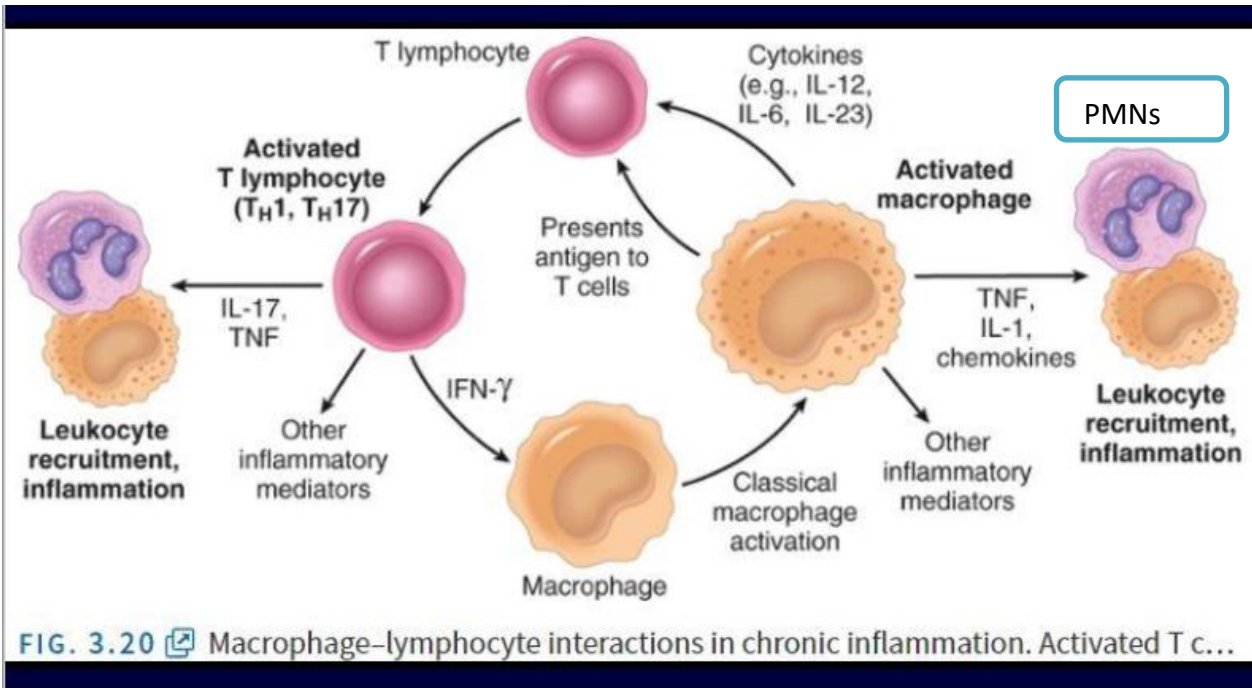
LYMPHOCYTES

- T,B lymphocytes
- Get activated by many factors, include microbes and environmental antigens .
- Viruses stimulate T lymphocytes mostly (viral illness shows less fever, leukocytosis are less, in tissue you find more lymphocytosis than neutrophils). Bacterial infections usually appears by increasing in B cells and neutrophils.
- In chronic inflammation lymphocytes are more abundant than plasma cells or Macs. Chronic inflammation in LUNG, TONSIL, INTESTINE have T lymphocytes more.
- CD4+ are T-helper lymphocytes, CD8+ are suppressor cytotoxic T lymphocytes.
- B cells mature to plasma cells secreting immunoglobulins (usually in bacterial infection).
- Lymphocytes secrete lymphokines

T-helper cells types are up to 20 and more. Most important:

1. **T-H1**: secrete (interferon gama), that activate Macs in M1 pathway.
2. **T-H2**: secrete IL-4 & IL-13 activate Macs in M2 pathway. Secrete IL-5 activating eosinophils in allergy (for example: Hodgkin's lymphoma cancer is caused by eosinophil recruiting).
3. **TH17**: secrete IL-17 (acute mediator for recruitment of PMN and monocyte) and induce chemokines.

TH1	INF-γ, activates Macs in classic pathway
TH2	IL-4, IL-5 & IL-13; activates eosinophils and Macs alternative pathway
TH17	IL-17 , induce chemokines secretion and recruits PMNs



Again all cells collaborate between hematopoietic cells and PMNs and Macs, which is very close, you can't separate them.

- Macs secrete TNF & IL-1 to recruit leukocytes
- Macs secrete IL-6 / IL-12/ IL-23 for activating T lymphocytes (go back to table 3.7)
- T cell secrete IFN-γ for activation of Macs in M1 pathway, IL-17 & TNF for recruitment of leukocytes.

EOSINOPHILS

- The name due to their color, pinkish granules
- Often 2 nuclei
- Diameter is 3-4 times of R.B.C
- They have granules that secrete IgE (allergic mediator)

Ex. Broncho asthma is caused mainly due IgE release.

- Parasitic diseases = more eosinophils
- Granules contain major basic proteins toxic (radical substances too) to parasites.
- May cause tissue damage
- Recently pathologists have determined specific type of chronic inflammation, (non-specific = Macs & lymphocytes & plasma cells).

Two types of specific chronic inflammation in this lecture:

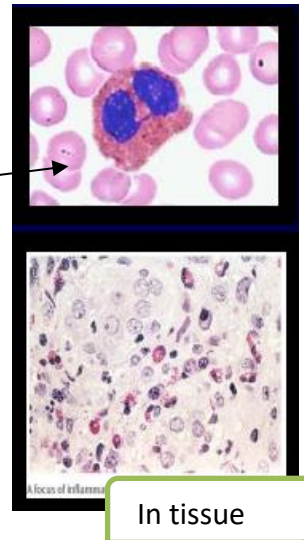
Eosinophilic inflammation & Granulomatous

Ex.

(Identifying under microscopes) for children who come with vomiting and loss of weight, they find change in lower part of esophagus (المريء), they find a red rings, if we look under microscopes it will appear tones of eosinophils = eosinophilic esophagitis

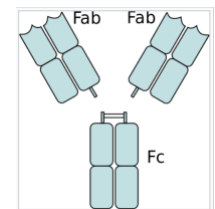
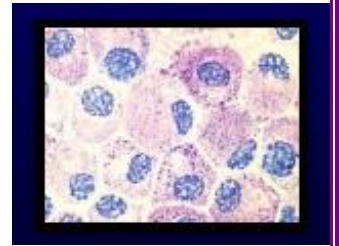
- Some scientists say that the chronic disease may contain an elements of allergy

R.B.C



MAST CELLS

- Scientists don't know many details about their function.
- **Abundant in** soft tumor tissues, fibroid in the uterus.
- **Active in** both acute and chronic inflammation
- Have a lot of **large granules** (little pink\ purple)
- MC(mast) and basophils **express** FcεRI (Receptor for Fc) binds with Fc portion of IgE leading to degranulation releasing of Histamine and PG of their granules. In (food allergy, venom **السّم**, drug allergy).
- In chronic inflammation, cytokines



FC portion of antibody

NEUTROPHILS IN CHRONIC INFLAMMATION:

1. Can stay for longer after acute inflammation (due to persistent microbes or continuous activation by cytokines (remember IL-17)).
2. Chronic osteomyelitis (inflammation of bone marrow) is very bad disease, so acute osteomyelitis is a medical emergency we should treat it early (next semester we will study it **إن شاء الله**).
3. Lung damage by smoking
4. If there is a background of chronic disease and then infected by an acute (acute on top of chronic) ex. Chronic active gastritis means that the disease is chronic and acute one has come. Chronic active pancreatitis = chronic disease and an acute visited the body 😊

Four chronic diseases special infiltration for PMNs

GRANULOMATOUS INFLAMMATION

“Please all of you, you must understand everything about this topic – extremely important “- Dr.Mousa

- A form of **specific chronic inflammation**
- The tissue in this situation is infiltrated by Granuloma
- Granulomas are collection of activated macrophages (bigger than monocytes, more active, more granules, can kill more, smaller nucleus...) & few lymphocytes and sometimes plasma cells.
- In histology, activated macrophages =(epithelioid hisitocytes)
Why epithelial?
epithelial = small nucleus & abundant cytoplasm, ioid = like
- Caseating means حليب الفاسد in old days, when they had a patient with tuberculosis , his lung fill with white nodules squeezing them appears a casein material.
- We should know the difference between this inflammation types:

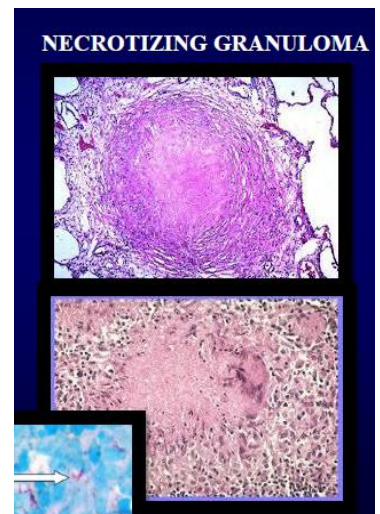
Necrotizing (caseating) (central necrosis) vs **non-necrotizing** (no necrosis)

Immune granulomas (can see them in certain type of auto immune disease like rheumatoid arthritis) vs **foreign body type** (granuloma formed around a foreign body)

"لا تتجاوز عن المفاهيم ببساطة" - دكتور موسى

Necrotizing granuloma

- In the middle of granule its pink= no nucleus
- The common type of infections that cause it is Tuberculosis
- Bacterial disease
- Can occur in any place
- The 1st picture is lung tissue , the 2nd is for lymph node

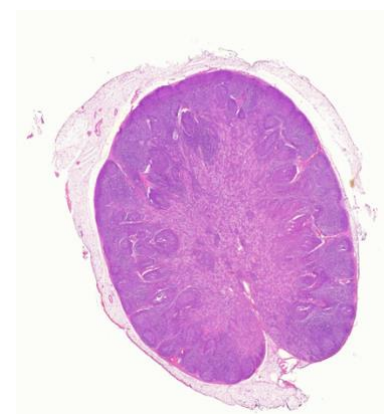
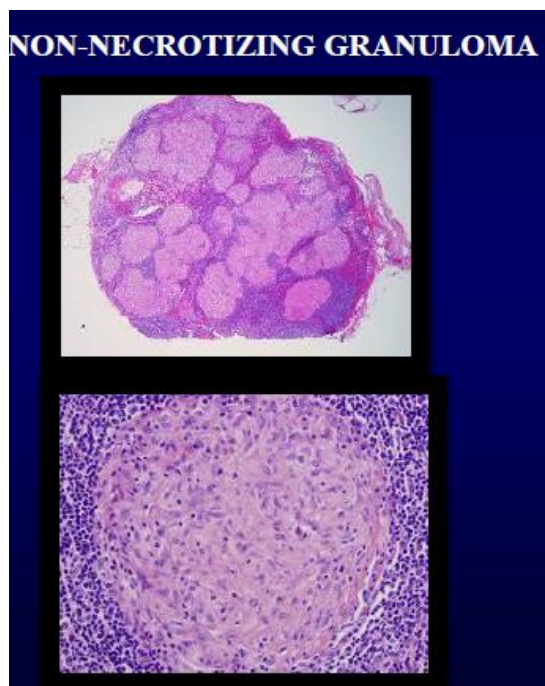


For extra detection we use special type of stain (fungal, TB tuberculosis) = Ziehl Neelsen stain (acid fast stain), the background of stain is blue, if there is bacilli it will be pinkish color

Extra : Ziehl-Neelsen staining is a bacteriological stain used to identify acid-fast organisms , mainly mycobacteria

Non-necrotizing granuloma

- This a lymph node
- Normally its blue with lymph nodes follicles, but here it's been replaced by granuloma.
- No necrotizing center (there are nuclei in the center)



Normal

As usuall another table to memorize 😬

H.W, read about cat-scratch disease, find the cause agent?

Ans. 😊

Bartonella henselae bacteria, kittens younger than 1 year are more likely to have it. Most cats show NO infection signs. 😞

Mentioned in the table below ..

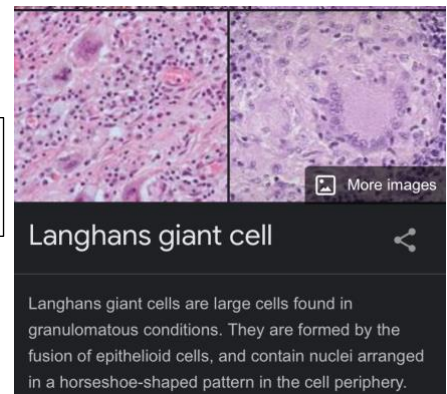


TABLE 3.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. Prolonged inflammation results in damage to the GI tract.



Summary

Chronic Inflammation

- Chronic inflammation is a prolonged host response to persistent stimuli that may follow unresolved acute inflammation or be chronic from the outset.
- It is caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, attempted repair by scarring, and immune response.
- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a morphologically specific pattern of chronic inflammation induced by T cell and macrophage activation in response to an agent that is resistant to eradication.

Some Que. From (2020 mid)Testbank:

1) TNF is a:

A-Cytokine

B-Chemokine

C-Lipid

D-Complement protein

2) -Which of the following cells and molecules are involved in asthma?

A-IgE and eosinophils

B-Cytokines

C-Macrophages and neutrophils

D-Complement proteins

3) A liver biopsy showed that a patient has a noncaseating granuloma. Which of the following disease can cause this condition?

A-Tuberculosis

B-Sarcoidosis

C-Syphilis

D-Asthma

4) -Which of the following is true regarding M2 pathway?

A-It is also called the classical pathway

B-It is activated by the presence of microbes

C-It stops inflammation and promotes repair

D-Macrophages start producing IL-1 and chemokines

5) A tissue biopsy from the colon for one of your patients who suffered from diarrhea was taken. The pathologist calls you and is worried about a parasitic infestation. The most likely inflammatory cellular infiltrate that he observed would be:

a. Lymphocytes

b. Plasma cells

c. Eosinophils

d. Macrophages

e. Eosinophils, fibroblasts and tissue macrophages.

ANSWERS :

1) A

2) A

3) B

4) C

5) C