11

Pathology

Doctor 2018 | Medicine | JU

Sheet Slides

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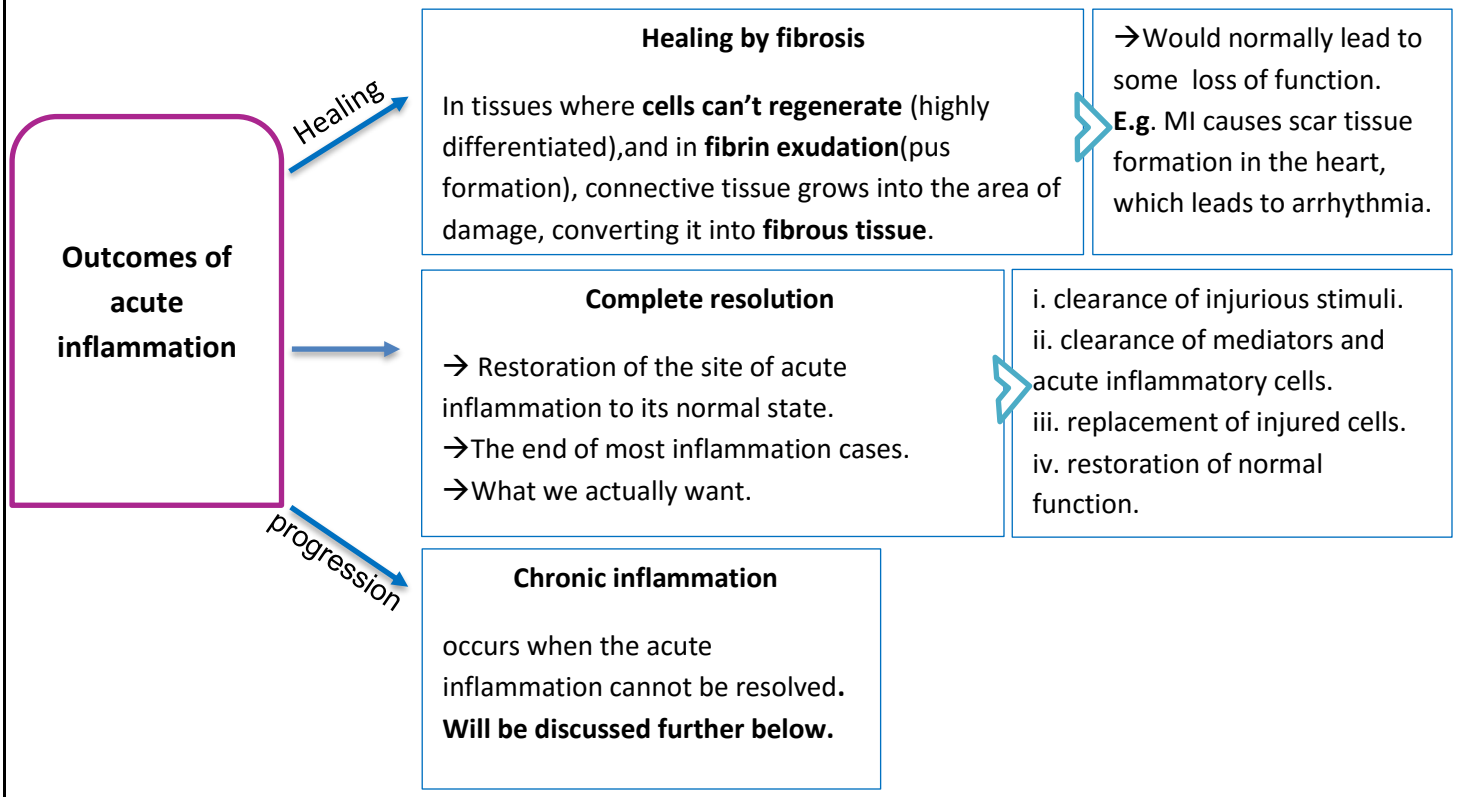
Remember when we talked about acute inflammation, we said it's a five Rs process, the fifth being **resolution.** But resolution is just the normal case of three possible outcomes of acute inflammation, how about we view them together?



Chronic inflammation:

• It's a **Prolonged inflammation** (weeks-months-years). In chronic cases, inflammation[1], tissue injury[2] and attempts at repair[3] coexist at the same time with varying degree.

• May follow acute inflammation but may be insidious or smoldering.

• Sometimes, it's progressive, it starts with a subclinical acute phase that doesn't declare itself, and it progresses silently.

• Main indicator of chronic inflammation is **tissue change**, whether it was accompanied with an acute phase or not.

Morphologic features of chronic inflammation:

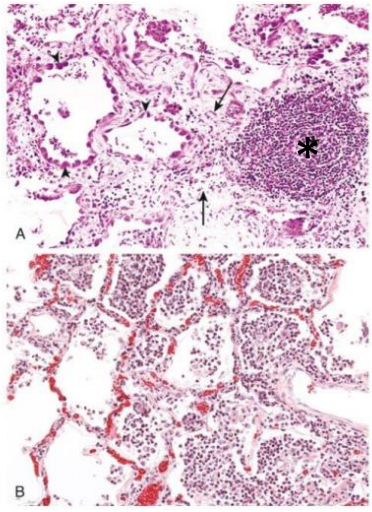
• Infiltration by chronic inflammatory cells (macrophages, lymphocytes & plasma cells)
• Tissue destruction
• Attempts at healing by angiogenesis (proliferation of blood vessels) and **fibrosis.**

Causes of chronic inflammation:

Persistent infections (pathogens known for their persistence)	Hypersensitivity diseases	Prolonged exposure to toxic agents	Other associated diseases
-Mycobacteria (TB) **-V**iruses (hepatitis C) **-F**ungi, parasites **-D**elayed hypersensitivity reaction (autoimmune) **-G**ranulomatous inflammation (will be discussed thoroughly in the next lecture)	- Rheumatoid arthritis. - Asthma (acute phases with some chronic features) -Multiple sclerosis **'May end in fibrosis of affected organs, which could end up in organ failure'.**	-**Exogenous**: silica (silicosis), ends up in lung cancer. -**Endogenous**: Atherosclerosis (cholesterol) -	-Alzheimer's -Metabolic syndrome of Diabetes Mellitus (screening by measuring abdominal girth), it increases risk of ischemic heart disease.

Stigma (signs) of chronic inflammation doesn't show until things are too bad, and tissues are damaged beyond repair..

We talked about **morphologic features** of chronic inflammation. Here is a demonstration of the <u>difference</u> between **chronic** inflammation's effect and **acute** inflammation's effect.



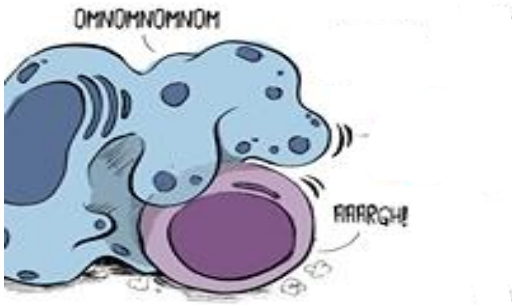
The picture shows **lung alveolar section**, in the case of **chronic inflammation**. There's tissue structural change, collection of chronic inflammatory cells* in what's known as tertiary lymphoid structure, and apparent destruction of parenchyma (cell type change, fibrosis).

This picture shows alveolar tissue in **acute inflammation** (acute **bronchopneumonia,** a killer in elderly patients), structure still has the same appearance, but we have many neutrophils filling up the alveolar space, blood vessels are congested and prominently showing.

Cells and mediators of chronic inflammation:

Macrophages and **lymphocytes** are the major role players. They are at continuous communication with each other through interleukins. Other cells like **Eosinophils** and **mast cells** can be cellular infiltrates in chronic inflammation, with certain functions.

Macrophages:



- Secretion of mediators (TNF, IL-1, Chemokines..)
- Feedback loop with T cells
- Phagocytosis
- Origin: circulating monocytes (1-day half life)
- Tissue Macrophages: Kupffer cells(liver), sinus histiocytes (lymph nodes), alveolar macrophages (lung) & microglia (CNS) together they make up the (mononuclear phagocytic system). Half-life = months (they survive longer once they enter tissue)

Activation of Macrophages occurs through two pathways:

M1, the classical pathway and M2, the alternative pathway

But first, we need to differentiate between monocytes and their activated macrophages:

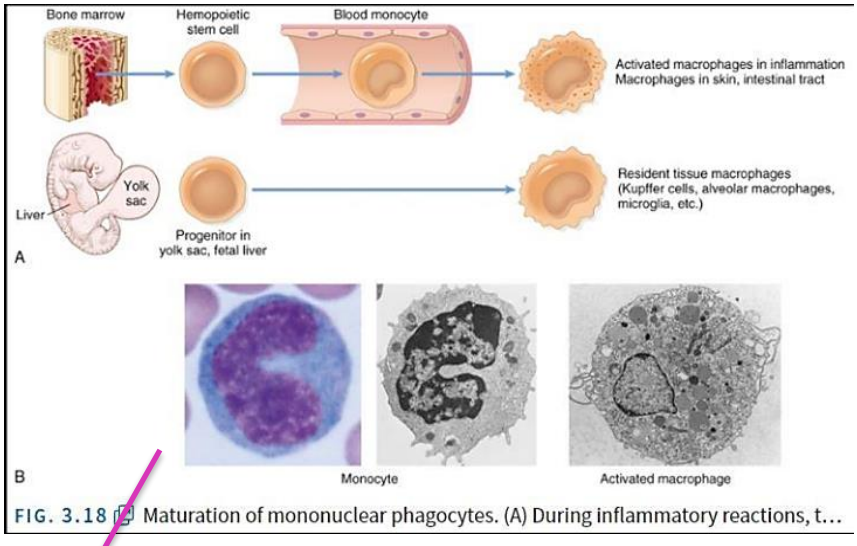


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

- at the **stem cell** stage, cells have **different structural morphology** than when they **mature**. This difference is presented by N/C ratio (nucleus to cytoplasm). At the **beginning** this ratio would be **high** because the nucleus occupies most of the cytoplasm, and not many organelles are present (i.e. in primitive cells), as **cells maturate and differentiate further** the nucleus gets smaller and other organelles become more abundant among the cell and N/C ratio becomes **low**.

Now look here, even at the early stages of maturation (monocyte) the nucleus is big in the cytoplasm, but as it differentiates further into a **macrophage**, the nucleus gets smaller.

What about activation (terminal differentiation) of monocytes into macrophages?

→We mentioned before that it has two major pathways, *classical* and *alternative.*

These pathways, differ by three things:

a. The environment that drives their occurrence.

b. The mediators that cause the specific differentiation of the macrophage (nature of activating signal).

c. Action of the activated cell, more specifically the mediators it produces.

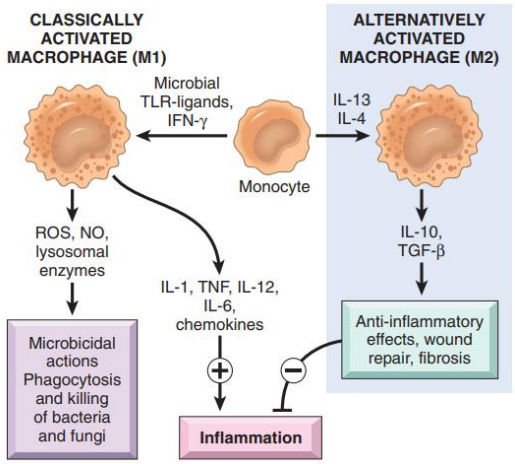
The *Classical Pathway*:

Macrophages activated by this way are important in host defense **against microbes** and in many **inflammatory reactions.**

Activators of this pathway are microbial TLR-ligands (e.g. endotoxin) and IFN-ℊ which is a T- lymphocyte signal.

When cells undergo this pathway, they produce two types of agents:
1. **Microbicidal agents:** like ROS, NO and lysosomal enzymes. (phagocytosis and killing of bacteria and fungi)
2. **Inflammatory mediators**: like IL-1, TNF, IL-12, and chemokines.

The effects of this pathway are called **proinflammatory**, meaning they upregulate inflammatory responses.



The *Alternative Pathway*:

Its inducers are **IL-13** and **IL-4**
It takes place once the pathogen is neutralized.

When cells undergo the alternative pathway they produce IL-10 and TGF-β.

These mediators have anti-inflammatory effects completely opposite and neutralizing of the classical pathway.

They induce tissue repair by secreting growth factors that promote angiogenesis, activate fibroblasts, and stimulate collagen synthesis.

It makes sense that in response to most injurious stimuli, the **first activation pathway** is **the classical** one, designed to destroy the offending agents, and then it's followed by **alternative activation,** which initiates tissue repair. However, such a precise sequence is <u>not well documented</u> in most inflammatory reactions. So don't bother with <u>when</u> for now, just understand the mechanism and know the mediators.

The role of lymphocytes (especially T-helper cells):

• T & B lymphocytes get activated by microbes and environmental antigens.

• They are the main cells seen in tissue with chronic inflammation

• CD4 +ve T-cells secrete cytokines inducing inflammation (T-cells are nearly the owners of communication molecules "cytokines")

*CD4 is like a cell surface antigen (protein) that characterizes a certain type of T-cells

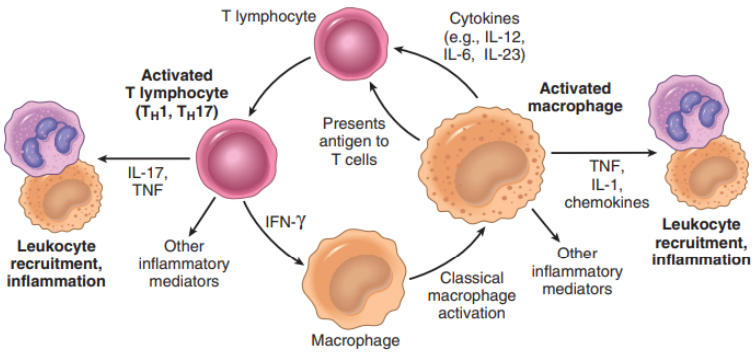
• B cells and plasma cells

We know that we have two main subtypes of T-cells, helper T cells and cytotoxic T cells. They're known as CD4+ T-helpers and CD8+ T-suppressors, respectively.

CD4+ cells are our stars in this context, because they work in mediation of inflammatory response.

They have many subtypes, of which three are what hold the most importance here:

T_H1	**Produce IFN-ℊ and others, which are most abundant at early stages of inflammation, they activate microphages in the classic pathway (M1).**
T_H2	**Produce IL-5 (which recruits eosinophils in acute allergic reaction and parasitic infection), IL-13 which activates eosinophils and macrophages in the alternative pathway (M2) & IL-4.**
T_H17	**IL-17, which induces chemokines secretion and recruits PMNs, mainly neutrophils in acute inflammation; trying to protect the architecture of the tissue.** **Doesn't induce neither M1 nor M2 macrophagic activation pathways.**



This is gift no.2 from the doctor ☺

→ T-cells and macrophages have continuous communication with each other.

This continuous communication propagates chronic inflammation.

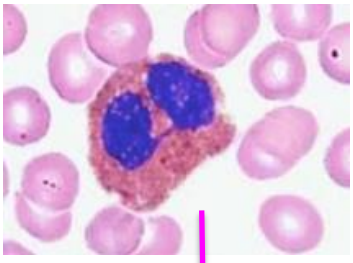
About the picture above:

Macrophages display antigens to **T-cells**, and express membrane molecules that **activate T-cells**, and produce cytokines (IL-12, IL-6, IL-23) that also **stimulate T cell responses.**

Activated T lymphocytes, in turn, produce cytokines (e.g. IFN-ɣ), which **recruit** and **activate macrophages**, promoting more antigen presentation and cytokine secretion.

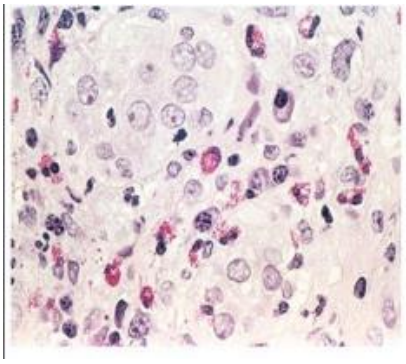
The result of this is a cycle of cellular reactions that fuel and sustain chronic inflammation.

Eosinophils:



Morphologic features of eosinophils:
- **two** nuclei
- **eosinophilic** granules.

- Abundant in immune reactions mediated by IgE and in parasitic infections.
- Granules contain major basic proteins toxic to parasites
- The toxin mentioned above could cause damage to host's epithelial tissue.
- Eosinophils are strong in immune reaction against parasites but ☹ they also contribute to tissue damage in immune reactions like allergies.
- Eosinophilic inflammation. These cells act as chronic inflammatory cells, an example of a case where we can find them abundantly is in conditions called (**eosinophilic -itis**).



An example the doctor gave was **eosinophilic esophagitis, in this case** if we did a laparoscopy, we would find circular rings at the lower esophageal portion. a histologic study of a section in it, would reveal presence of many eosinophils (e.g. 8 in the picture up there ↗).

GOOD LUCK