Doctor022

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PATHOLOGY

Sheet no. 3

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Transmigration

The last lecture we finished talking about the initial vascular phase (vasodilation) due to histamine, then the more active process which increase vascular permeability, then the movement of the inflammatory cells (mainly neutrophils and microphages) from the intravascular compartment to the extravascular compartment.

we detailed this process from margination ➡️ Rolling ➡️ initial selectin (weak attachment) ➡️ Stronger integral attachment to the wall of the endothelial cells ➡️ then the active process of transmigration (diapedesis) due to CD31 (PECAM-1) which use the collagenase to destroy the basement membrane and movement of the cells to outside.

Chemotaxis

This term you will hear it from now to start dealing with patients, in cases of inflammation, pneumonia and dermatitis, etc...

🔴 Remember that the (tis) is the term we use to describe the inflammation of the organ, like:

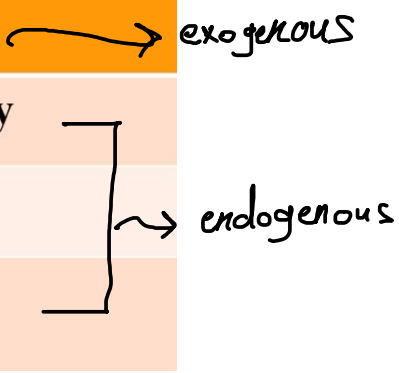
Appendix ➡️ Appendicitis

Tonsil ➡️ tonsilitis

So .. what is chemotaxis?

basically, is the movement of white blood cells to the site of injury, as for example, if the injury is in your tonsils the WBCs will move to your tonsils. It's an active process, inducing by certain mediators. These mediators all together named chemoattractant, they are classified as exogenous* from outside the body or they are endogenous* produced inside the body. Also, some of them are bacterial products, especially the n terminal of the peptide of those products. And they are actually strong chemoattractants who induce the WBCs to move from the intravascular compartment into the site of injury.

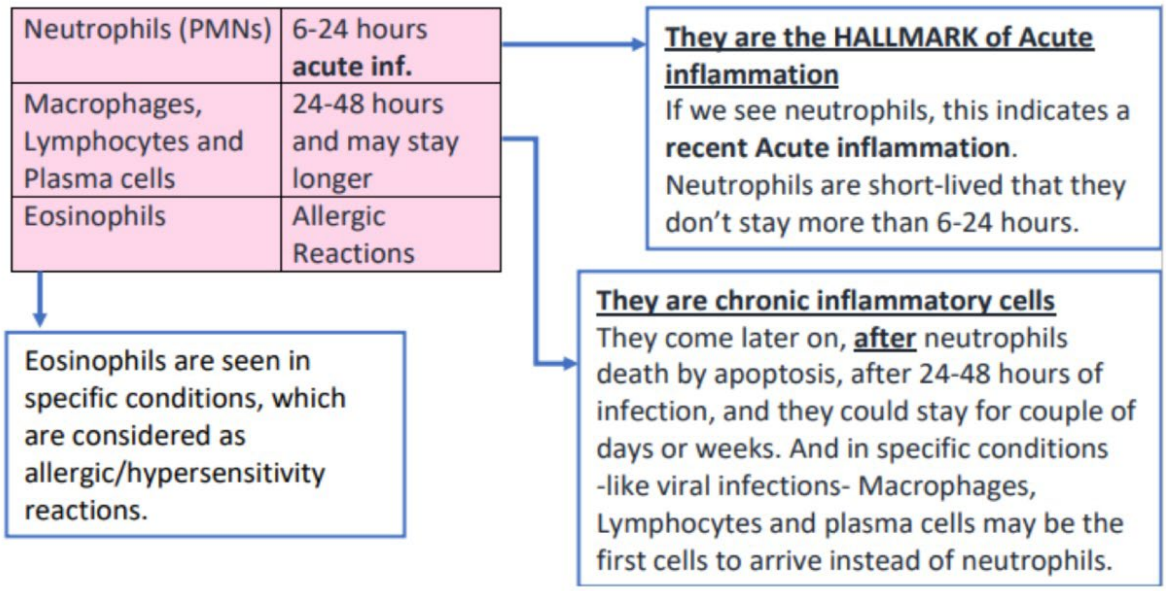
Bacterial products	Peptides (N-…)
Cytokines	Chemokine family
Complement system	C5a
Lipoxygenase pathway AA	LTB4



- Cytokines: a big group of mediators released by inflammatory cells, mainly lymphocytes and macrophages, especially the chemokine family, and this family is a subgroup from cytokines and considered as the strongest family.
- Complement system: plasma proteins in our system act as chemoattractants, and complement 5 a (C5a) is the strongest among the complement system.
- Lipoxygenase pathway Arachidonic acid (AA): this group comes from arachidonic acid metabolites, which is a part of cell membrane component, LTB4 (leukotriene B4) is the strongest chemoattractant among the AA metabolites.

WBCs infiltrate in the tissue

The movement of WBCs from the intravascular to the tissue, depends on the age of inflammatory response and the type of stimulus as shown in the table below:



These are some cases, enjoy reading them 😃

1- A 15-year-old girl came to the clinic suffering from pain around the umbilicus, then it radiated to right iliac fossa. She was diagnosed with acute appendicitis, and she managed by appendectomy.

The sample (appendix) was examined by pathologists, they found neutrophils in, this proved the diagnosis (appendicitis).

2- A 39-year-old man came with spasm and the doctor gave him ibuprofen (مسكن) and let him leave, after 6 hours the patient died, by investigations pathologists took section from the heart and they found neutrophils which indicates that he suffered from acute myocardial infarction.

Let's now look over some histological micrographs:

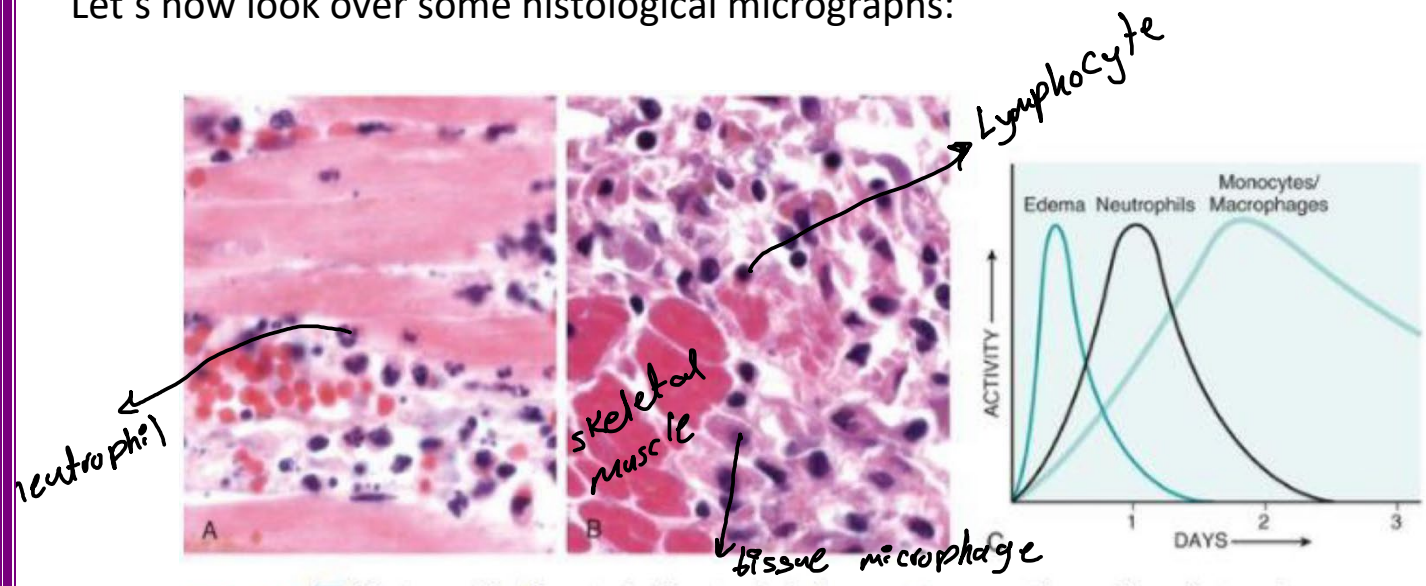


FIG. 3.5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrograp…

A. Alot of neutrophils, or mickey mouse cells as doctor named them, so this is an acute inflammatory process which indicates that those morphologic changes took place within the last 24 hours, Early (neutrophilic) infiltrates and congested blood vessels. So, this is a histological section for acute inflammation.

B. Mononuclear cells infiltration is shown, which indicates that this is the chronic phase of the inflammation, later (mononuclear) cellular infiltrates.

C. This diagram shows many phases:

-Edema: first phase (vascular phase) where edema starts to appear.

-neutrophilic infiltration: second phase, where edema starts to go down in one and a half day, then the recruitment and stimulation of chemotaxis of neutrophils to the tissue of injury start early and end the second day

-monocyte, macrophage and plasma cells: those are chronic inflammatory cells, and they take longer time to clear up.

Now I'll show you image, it seems complicated but don't worry you will know just 🧐 رؤوس أقلام

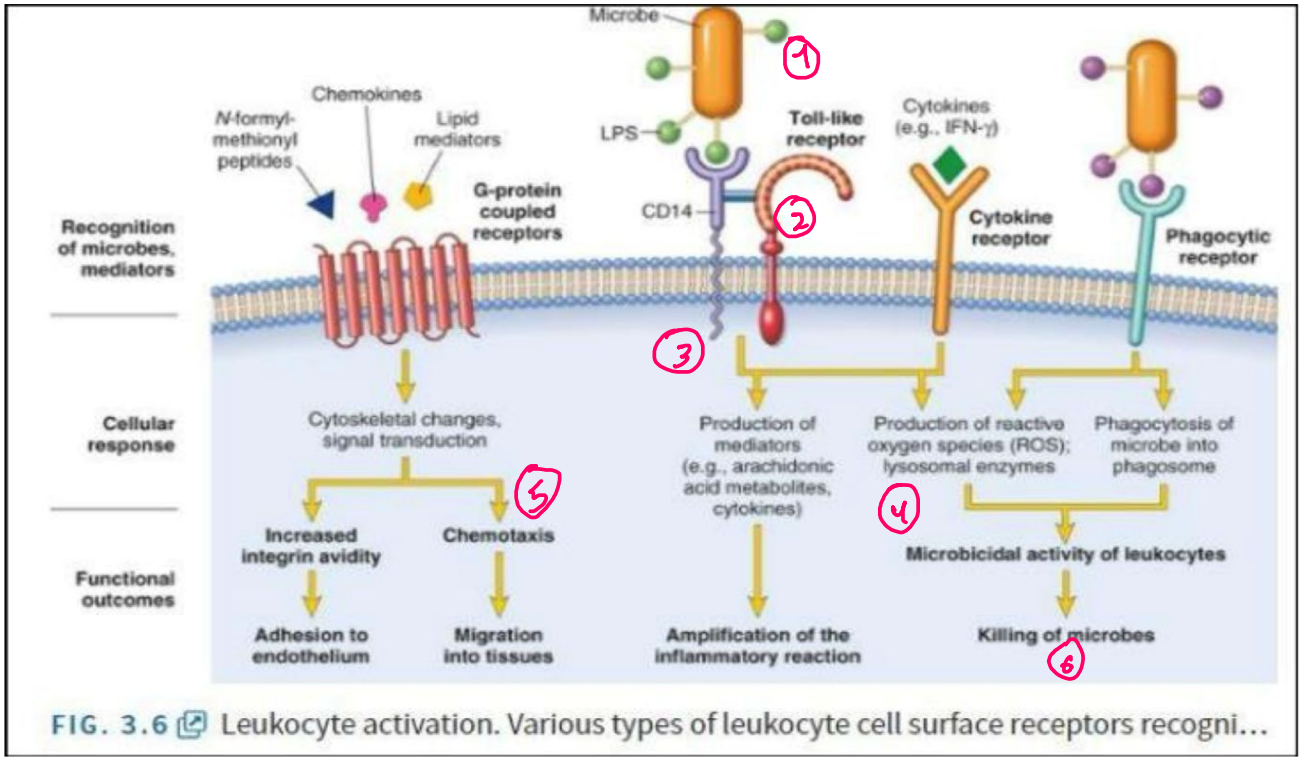


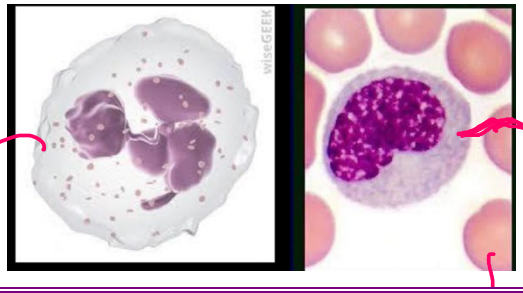
FIG. 3.6 Leukocyte activation. Various types of leukocyte cell surface receptors recogni…

1. Firstly: recognition of offending agents (bacteria, virus,...)
2. Stimulation through certain receptors for example: Toll-like receptor, it has 3 domains (extra cellular domain, intramembranous domain, intracytoplasmic domain).
3. Then the message enters
4. Activation
5. Chemotaxis
6. Killing microbes

➡️ the initial inflammatory phase there will be release of too many chemical mediators from multiple sources to amplify the inflammatory reaction so the killing of microorganisms will be so efficient.

Leukocyte activation:

It's important in initial phase of inflammation, the two major cells for this phase are macrophages (monocyte) and neutrophils.



-Neutrophil: multi-nuclei and granules

-monocytes are macrophages but they are circulating, once they inter the tissue, they become tissue macrophages. They have kidney-shaped nucleus and less granules.

Phagocytosis and intracellular killing are the main functions for neutrophils and macrophages.

So, Leukocyte activation mainly results in:

- Phagocytosis.
- Intracellular killing/destruction of phagocytosed microbes and dead cells.

Phagocytosis:

It's multi-step process as shown in the picture below:

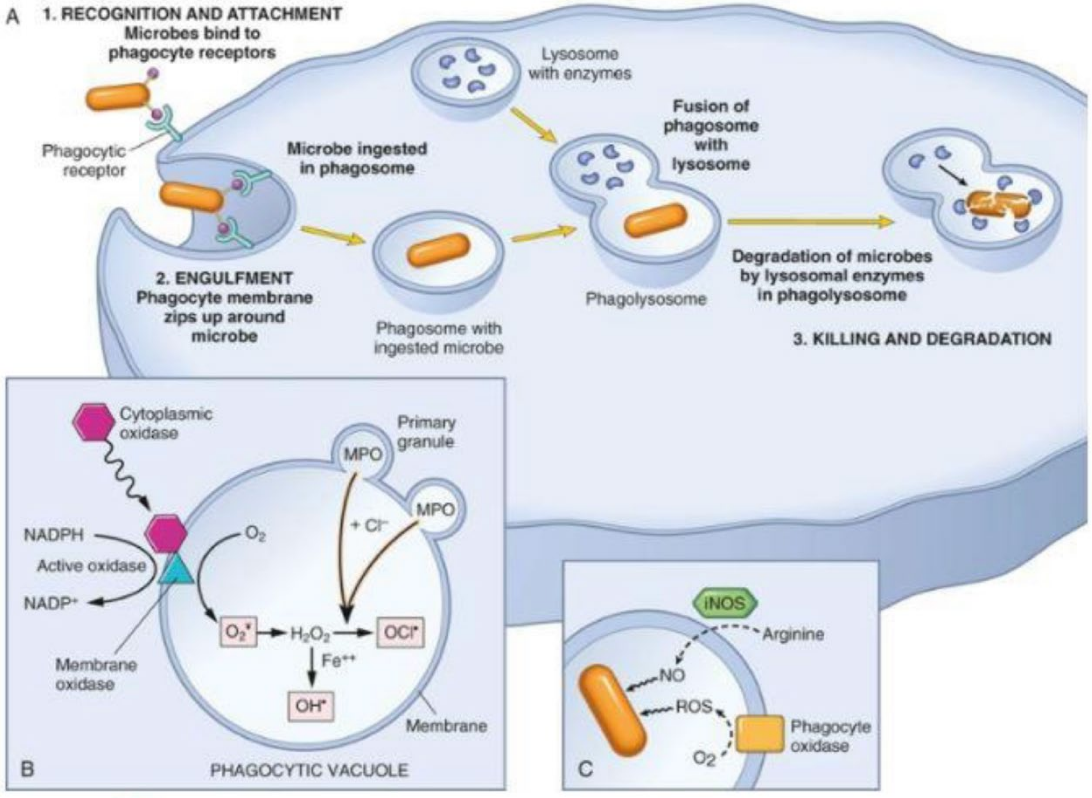


FIG. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a p…

Let's discuss each step:

1. Recognition and attachment of the enemy (bacteria, virus...): mannose receptors; opsonins (IgG, C3b "strong opsonizing agent")
   Opsonization: increasing the efficiency of phagocytosis (intracellular killing, R3 in inflammatory response)
   Without the opsonizing agent (IgG, C3b), the intracellular killing will be weak, so disease prolongs and makes more recurrent infections.
2. Engulfment forming phagocytic vacuole: phagosome phagosome: is a part of the membrane of the neutrophil or macrophage that surround the bacteria or virus.
3. Killing & degradation: reactive oxygen species (ROS); NO. H202- MPO-halide is the most potent bactericidal system of neutrophils

NOTE:

Every step of these steps has a chemical mediator that stimulate it, in other words every step needs activation.

Phagolysosome: the process in which lysosome fuse with phagosome which helps in degradation of microbes.

لا تنسوا أهلنا في غزة من دعائكم 🫶

And remember:
Never lose hope, you will be someone's hope ... someone's hero
💖

Now, let's talk a little bit about:

NITRIC OXIDE (NO)

In the last 10-15 years, it attracted a lot of attention in research. There was a lot of good knowledge originated from the discovery of NO.

- **It's a soluble gas produced from Arginine (amino acid) by an enzyme called NO synthase (NOS).**
- **There are 3 types of NOS: eNOS, nNOS, iNOS.**

- **iNOS is responsible for intracellular killing stimulated by cytokines mainly IFN-ℵ (interferon gamma).**

IFN-ℵ is one of the cytokines. Now, they are being utilized as a target therapy certain inflammatory autoimmune disease, cancer treatment.

- **NO reacts with superoxide (O2-*) to form ONOO* radical peroxynitrite (very strong).**

GRANULE ENZYMES

*Remember: macrophages and neutrophils both have granules. Though, neutrophils are more heavily granulated.

- **Present in PMNs (polymorph neutrophils/nuclei) and monocytes.**
- **In PMNs: 2 types; large azurophil granules (primary) and smaller (secondary) granules.** The name: "azurophil" was given after the dye.
- **Primary G: contain MPO (Myeloperoxidase), other enzymes** which are needed in the intracellular killing.
- **Secondary G: contain lysozyme, and others.**
  - And they are the ones which are utilized after the production of the phagolysozyme in the later stages of phagocytosis.
  - They can be injurious if not controlled, so:
- **They are usually neutralized by antiproteases (such as ἀ-1 antitrypsin: inhibits elastase).** If one has certain diseases or ἀ-1 antitrypsin deficiency -especially in the GI tract- there will be no inhibition of those lysozymes and enzymes released by neutrophils and macrophages and this will induce injury and chronic diseases.

NEUTROPHIL EXTACELLULAR TRAPS (NETs)

- **Viscous meshwork of nuclear chromatin binds peptides and anti-microbial agents after PMN death (NETosis).**

So, even after the neutrophil dies and ruptures the chromatin material and the intracytoplasmic (inside) and the intramolecular material (outside) will cause a very thick meshwork of material which will help trap those bacteria or invaders at the site of injury, so they get killed by other still-viable neutrophils.

- **Sepsis.**
- **May be involved in SLE.**

Scientists discovered that NETs have a role in an autoimmune disease called: "systemic lupus erythematosus" or SLE مرض التذاؤب الاحمراريّ

SLE is a multisystem autoimmune disease that affects young females, giving them rash in their cheeks. It attacks the kidneys, heart, skin, joints…etc.

We will probably have a clearer idea about the NETosis process in the pathogenesis of sepsis and some of the autoimmune diseases in the next 5-10 years, Insha'Allah.

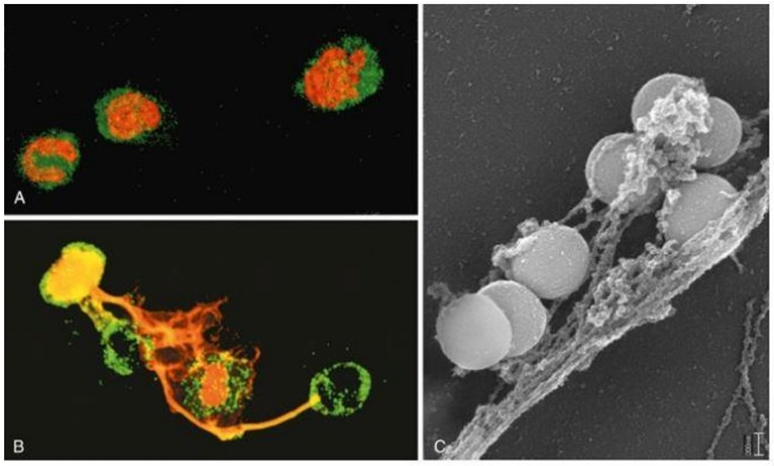


FIG. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stain…

The figure above represents a high scanning picture explaining that thick viscous material. (C): the spheres are bacterial cocci, and the sticky material is the NETs of the neutrophils. so they stick to those organisms so that they stay in a particular are, allowing other inflammatory cells to come and kill them.

(يعني ال NETs بيلزقوا بالبكتيريا وبيثبتوهم بمكانهم لعند ما تيجي more inflammatory cells تتخلص منهم)

LEUKOCYTE-MEDIATED TISSUE INJURY

We have just mentioned that you need the WBCs (neutrophils, macrophages) for your body's defend mechanisms to help you get rid of organisms. However, sometimes occurs an injury related to the infiltration of the leukocytes in tissue, if the response was too much. Each inflammatory process can leave some side effects or tissue injury. Which indicates that although inflammation protects you, it can be harmful sometimes in certain scenarios.

Examples of those scenarios:

A. Prolonged inflammation (TB an Hepatitis)

Mycobacterium tuberculosis is a very strong and violent bacteria which can induce prolonged inflammation causing tissue damage and injury.

Hepatitis C causes chronic liver disease from this prolonged inflammation. Chronic hepatitis C infection is the most common cause of chronic liver disease nowadays in the Middle East.

B. Inappropriate inflammatory response (auto-immune diseases)

This is the basic concept of autoimmune diseases, like: SLE (mentioned in the previous page), rheumatoid arthritis, mixed connective tissue disease. The basic mechanisms of those diseases is still a topic under study.

C. Exaggerated response (asthma and allergic reactions)

When the inflammatory response in disproportionate to the antigenic stimuli. And this is the basic mechanism for acute allergic reaction and bronchial asthma, where slight flu, cold, stress will induce exaggerated allergic reaction causing signs/symptoms/diseases.

OTHER FUNCTIONS OF ACTIVATED WBCs

We always need WBCs recruited to the tissue of injury, so there are additional functions which are committed by those cells:

- **Amplification or limitation reaction (cytokines)**

Cytokines can amplify the inflammatory reaction if needed. Like in 2nd or 3rd phases of inflammation we need more soldiers, recruitment, chemotaxis, because the enemy count is high. So the WBCs will produce cytokines to enhance the reaction. However, if we reach the point where most of the bacteria is dead (phagocytosed, killed by ROS inside macrophages) they will produce cytokine to limit/contain/terminate the inflammatory reaction.

- **Growth factors secretion (repair)**

Growth factors are extremely important in the late phases of inflammation, where "repair" starts. WBCs will secrete those factors which helps starting the repairing process.

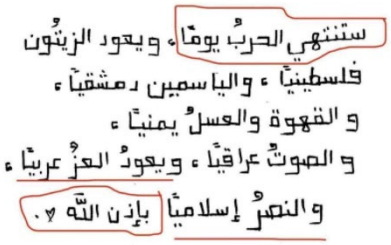
- **T-lymphocytes also have a role in acute inflammation (T-HELPER-17); produce cytokine IL-17 (deficiency cause disease)**

In the past, they used to think that T-lymphocytes have no role in acute inflammation. Years later, they found out that T-helper-17 cells play a major role. They produce a cytokine called interleukin-17. Deficiency of this cytokine causes disease, decreasing immunity.

TERMINATION OF ACUTE IR

At this stage, after we killed almost all of the organisms (bacteria, virus), we need to terminate the IR. We don't want it to continue and cause side effects. Those enzymes and mediators can injure the tissue as mentioned before. So the following phase is where our bodies control and stop the IR by these 7 major mechanisms below. Details next lecture, Insha'Allah.

Mediators are produced in rapid bursts
Release is stimulus dependent
Short half-lives
Degradation after release
PMNs short life (apoptosis)
Stop signals production (TGF-ß, IL-10)
Neural inhibitors (cholinergic): inhibits TNF



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