Doctor 021

PATHOLOGY

Sheet no. 7

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SYSTEMIC EFFECTS OF INFLAMMATION

• Any inflammation can be associated with systemic effects due to cytokines release " ACUTE PHASE RESPONSE"

all mediators can cause the systemic effects, but the most important mediator that can cause systemic effect(like: fever, general malaise, loss of appetite) is the cytokines.

Remember: cytokines are proteins not cells .

The doctor asked us to search about cytokine storm :

They are various(have been referenced in various infectious diseases like COVID-19) inflammatory cytokines are produced at a much higher rate than normal, and can cause systemic manifestations including hypotension, death,…

the patient will take anti-inflammatory agent.

some of them are the acute phase proteins that come from liver and theyare non-specific because they are produced in case of septicemia ,salmonella, and viral illness (they are just a marker for you to know what is going on? Are the patient get better or not?) for example if the C reactive protein measurement (in the serum)is high then the patient doesn't getting better .

- The acute phase response is predominantly mainly due to multiple cytokines secretion like :

(TNF, IL-1, IL-6, & type 1 interferons)

Type 1 interferons: It was just dealt with in cancer and pinealomas.

Fever (1-4 C) elevation	**Exogenous pyrogens (LPS) & endogenous pyrogens (IL-1 & TNF). All induce PGE2 secretion**
Acute phase proteins	**CRP, SAA, ESR, Hepcidin**
Leukocytosis (increase WBC)	**15-20 K if more than 40 (leukemoid reaction), left shift**
Others	**Tachycardia, Increase BP, Chills, Rigors, decreased sweating, anorexia, somnolence, and malaise**

_SAA serum analoid A, ESR erythrocyte sedimentation rate .

Leukemoid __ شبيه بالسرطان

1- **Fever:** Normal body temperature is (36.1-37.4°C). Any increase above this range (usually by 1 to 4 degrees) is considered a fever. That is caused exogenous pyrogens LPS (lipopolysaccharide of the bacterial wall itself)or by endogenous pyrogens (IL-1 & TNF they are cytokines)

Pyrogens: they cause pyrexia (fever)

PGE2 secretion: prostaglandin secretion.

2-Acute phase proteins: C reactive protein (CRP),SAA ,ESR ,Hepcidin :they are all non-specific

3- Leukocytosis (increase WBC) : when the patient have bacterial infection (acute appendicitis, tonsillitis ,gastritis) the cytokines will go to the bone marrow and induce hematopoiesis (leukemogenesis)

the leukocytosis increases in the bacterial infection but it can also happen in the viral infections

for example: if the patient come and his tonsils have white dots (exudate)this is bacterial infection ,the white blood count is 25-30 Leukocytosis and when you make a differential count, the neutrophils will be in high amount(neutrophilia) , so neutrophilia with leukocytosis will result in bacterial infection.

In viral illness the leukocytosis will be low and they have a high amount of lymphocytes ,these are general roles, and of course there are some exceptions like salmonella (there is neutropenia although its bacterial infection).

The normal number of WBCs in the blood is 8-11 thousand cells. In acute inflammations, this number increases to 15- 20 thousand cells by mediators acting at the bone marrow for the synthesis of more WBC'S. Sometimes, we notice that the number can go up to 40, 50 or even 100 thousand. These extreme elevations are referred to as leukemoid reactions because they are like leukemia. To distinguish between leukemia and leukemoid reaction, you do the white blood count and the white blood count is 45000 and you look at the differential count it has many neutrophils, most of the time it's a leukemoid reaction, this is when we take the sample to a certain machine to see whether the cells are monoclonal (cancerous) or polyclonal (not cancerous and the body simply gave an exaggerated response). Leukemoid means leukemia-like. So, it's not really malignancy. However, you must do

investigate these by specific delineation by immunophenotyping of the peripheral blood white blood cells to make sure that those are nonneoplastic white blood cells. We do usually flow cytometry in those to reassure the patient they were only leukemoid reactions. So, this is an exaggerated response as a systemic effect inflammation called leukocytosis.

Note :there are overlaps in the mediators functions, but we talk about main actions of them.

4- Others :

Chills : are your body's way of raising its core temperatureرجفة خفيفة

Rigors: Severe chills with violent shivering رجفة أقوى

* definitions from google

SEPSIS & SEPTIC SHOCK

Sepsis, septic shock, and septicemia indicate severe acute bacterial infection which may be fatal (It's a common disease, you will see it mostly like in the different sectors of ICU) ,you have to prove the precense of bacteria in the blood through **blood culturing** .

The presence of bacteria in the blood is dangerous because that will result in the presence of chemical mediators of inflammation including cytokines, and as we talked before the cytokines have a local systemic protective then the cytokines reach the level of systemic pathologic (like decrease cardiac output, hypotension) and that is the septic shock .

For example : if the patient shocked, his blood pressure 60\40 , the pulse is 130 and the temperature is 42 this is septic shock (serious state, and if he doesn't get treated Irwin we lose the patient).

Large amounts of mediators (TNF & IL-1) lead to multiple complications such as:

1. **Disseminated intravascular coagulation (DIC):**

A condition in which blood clots form**(**increasing in the prostaglandins and COX1 result in aggregation of platelets **)**throughout the body blocking small blood vessels causing multiple infarcts (Heart rate will go up…).

2. **Hypotensive shock.**
3. **Insulin resistance and hypoglycemia.**

All those features are features of septic shock and this is an acute emergency patient has to be treated quickly otherwise if he reaches to a

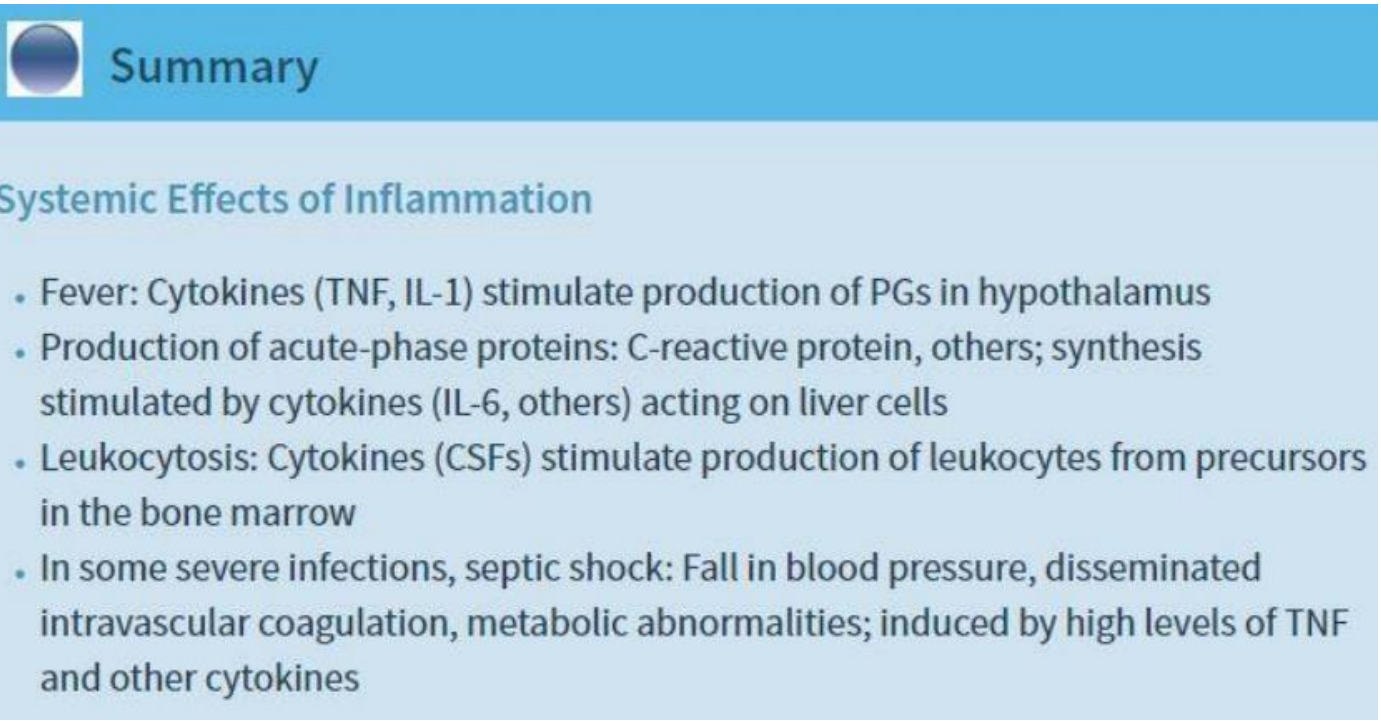
point of irreversible septic shock most of the time the patient will end up with multiorgan failure and then death.

NOTE: Gram-Negative sepsis is very dangerous.

Sepsis May be caused by non-infectious etiology: Pancreatitis, severe burns, and severe trauma.

All of these cases will have a lot of mediators impacting all your vital function causing a shock state(but they are not a septic shock, they are other types of shock) .

As sepsis develops due to mediators, the conditions described above fall under the category of “systemic inflammatory response syndrome” (SIRS). Probably this will be like the end result of too much acute severe inflammation with tissue damage and a lot of mediators and probably this is what's happening in Corona or Covid-19 nowadays.



TISSUE REPAIR:

we finished the lectures of inflammation and we will start the tissue repair lectures and they ‘re much more easier so let’s start 😊

** important reminder by Dr.Mousa “slides are not enough for the exam // All diagrams are required “ >> study hard …

Quick reminder … (R1) recognition (R2) recruitment (R3) elimination (R4) regulation (R5) repair (which is the topic of our lecture today)

so, the tissue repair process is part of the inflammatory response(R5) but comes at the end and sometimes it's given a separate entity.

- **Inflammation may cause injury and repair is critical after eliminating the enemy .**

whenever there is tissue injury there is repair even if it was very mild tissue damage ان شاءالله اربع خلايا بس خربانة لازم يصير—.

The repair depends on the intensity and duration of injury .(degree and amount) .

Keep in mind >> repair mediators = growth factors .

- **Repair can be achieved by:**
  - **1.Regeneration**
  - **2. Scar & fibrosis**

Both require mediators and cellular proliferation. And interactions with ECM.

*Regeneration is the preferred and the main mechanism of repair.

*Scar & fibrosis is replacement of the damaged tissue or parenchyma ;when regeneration is not possible.

-if the injury is very mild you may not feel the repair (intensity duration) .

Side note (from lec. 6)>>every chronic inflammation maybe presited by acute inf.or not but sometimes you may not feel the acute inf. (insidious) .

**Both of mechanisms requires chemical mediators of inflammation , cellular growth , cellular proliferation and critical complex interaction between the intravascular compartment , the cellular process of the inflammatory process , ECM and ECM proteins .

TISSUE REGENERATION:

- **Regeneration requires growth factors and interactions between cells and matrix(ECM).**
- **Tissue types**

Labile tissue	**Continuous regeneration : epithelia of mucosal surfaces**
Stable tissue	**Normally in G0, but can be stimulated to regenerate when injured (liver, Kidney, pancreas)**
Permanent tissue	**Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle)**

- Mucosal surfaces are usually exposed so it regenerates continuously by mitosis wherever it was (skin , GI tract , etc..) .
- Stable tissue are Solid organs> (Liver , kidney and pancreas..)
  If we remove part of it will grow again when it is stimulated .
- Permanent tissue once lost you can't replicate them, it will be replaced by scar tissue because the are very highly differentiated
- If a massive part of the organ is replaced by scar fibrosis this will lead to organ failure.
- In accedients they always say DO NOT move the injured person because you may cut (his/her) spinal cord {permanent tissue } it won't regenerate again .
- By new methods such as stem cells we may regenerate permanent tissue BUT at our level this method and all related studies and researches are not required لاااا تعقدوا الامور .

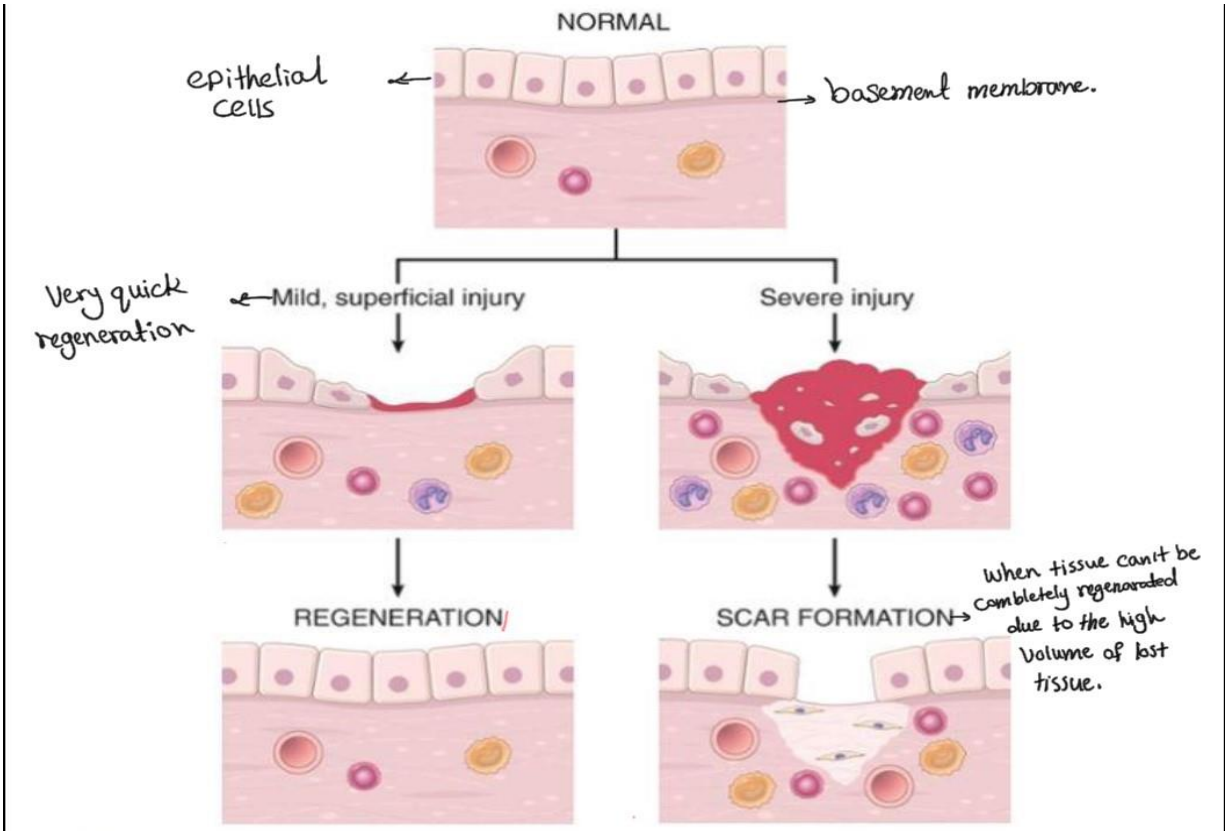


FIG. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mil...

- The degree of repair depend on the degree of injury .
- Injury on our face will be repaired quickly compared to injuries on our leg why ? Because they're highly vascularized ok but why ?? We will discuss this later(ANGIOGENESIS) 😄

LIVER REGENERATION:

• Liver can regenerate in 2 ways:

– 1.Hepatocytes proliferation, post partial hepatectomy

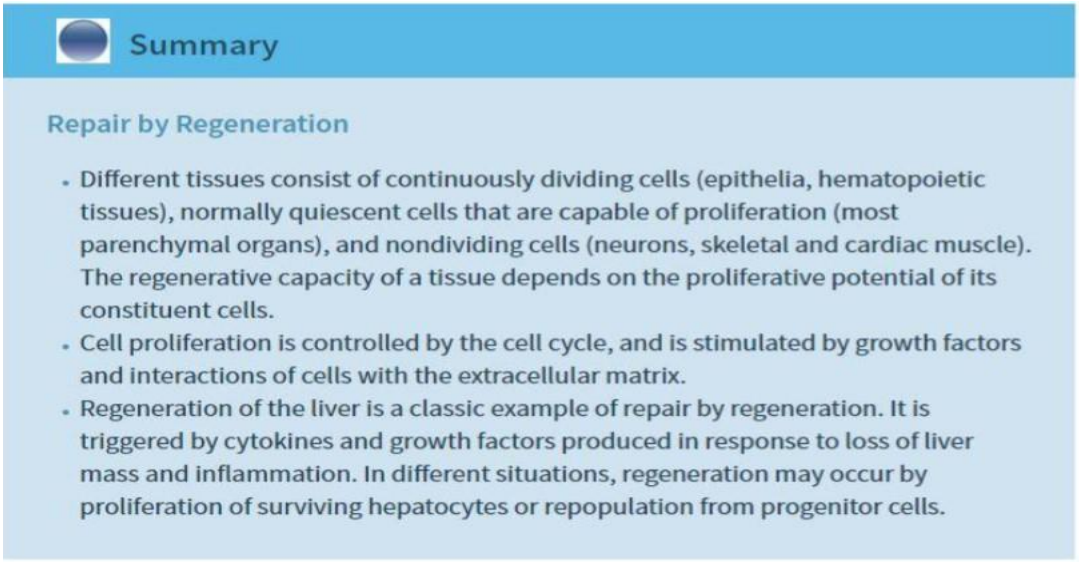
If there was liver parenchymal tissue damage regardless of the injurious agent ; whether it's a trauma or viral infection , the hepatocytes can proliferate and if we come back after six months the lost part of the liver has been replaced by a new liver tissue

– 2. Progenitor cells gets activated and proliferate and differentiate

Both need growth factors & cytokines and cell matrix interactions.

by recruitment of stem cells or Progenitor cells (found mainly in the bone marrow), (they get recruited and enter the microenvironment of the parenchyma then they have specific proper growth factors and mediators of that specific tissue), get activated then proliferate and differentiate.

** Both need growth factors & cytokines and cell interactions and matrix surrounding this tissue (proper environment)



REPAIR BY SCARRING:

- **Large amount of tissue damage**
- **“Patching”, wound healing and Scarring**

Healing by first and second intention

Two types of repairing (first and second intention)

#first intention

_In Small , mild superficial injury Like first degree of burn , scratch and surgical wound

-The reparative regenerative mediators will be stimulated

-The whole loss of superficial epithelium will be replaced by regenerating epithelial cells from the sites and they will fill into the gap specially if basement membrane is not injured or no deep injury was associated - its quick and takes less time -most of the tissue will go back to pre-

injury state (almost 98%)

#second intention

In severe injury -if somebody has crush accident with crush injury where there is a lot of tissue lost including the basement membrane , superficial epithelium, matrix and submucosal tissue

-The healing require granulation tissue formation and the amount of scar tissue which has been produced will be a little bit larger -sometimes disfiguring and embarks on the function of that organ -it takes longer time - The regeneration alone is not enough to fill in the gap

Steps:

– Hemostatic plug (platelets)…minutes

,(stabilization of your blood condition).

If you have normal platelets it will Occur within minutes

– Inflammation (Macs, M1 and M2)…6-48 hours

Switching between M1&M2 depends on (intensity & degree)

– Cell proliferation (granulation tissue)…10 days

If the wound was clean granulation will be minimal,,, this step include new blood vessel formation (angiogenesis), granulation tissue formation

– Remodeling…. 2-3 week

The extra tissue and material will be cleaned out and removed before the formation of strong scar tissue composed of strong collagen

replacing the damaged parenchyma.

Note : the amount of scar comparable to the amount of tissue produced

Eschar : hard dry fibrin clot mostly acellular which covers the lost tissue and prevents further bleeding

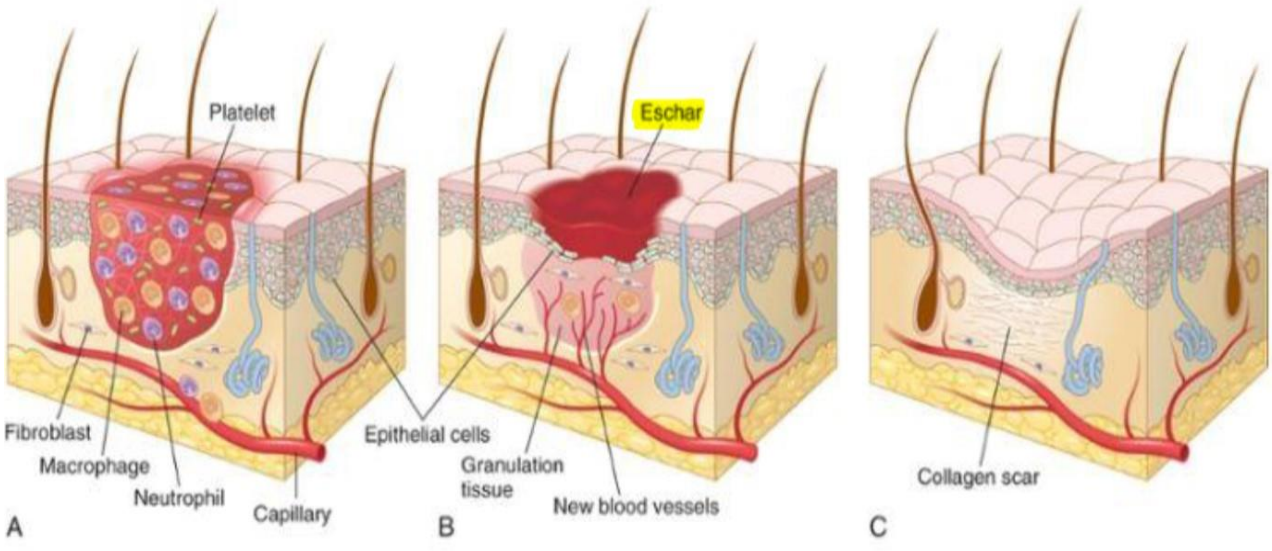


FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is …

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