Tissue types

Labile tissue	**Continuous regeneration : epithelia of mucosal surfaces**
Stable tissue	**Normally in G_0 but can be stimulated to regenerate when injured (liver, Kidney, pancreas)**
Permanent tissue	**Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle)**

- inflammatory response > injury > repair
- repair depends on the **amount** and the **degree** of damage
- It is critical step to eliminate the enemy and its consequences

Mechanisms of tissue repair

Regeneratio

requires:
1) growth factors
2) interactions between cells and matrix (ECM)

Called: healing by first intention

- for small/mild superficial injury.
- **quick**, more accurate.
- going back to pre-injury state.
- stimulate The reparative regenerative mediators > regenerating epithelial cells > replaced The whole loss of superficial epithelium.

-e.g: first degree of burn, surgical scar.

Liver Regeneration

In 2 ways:
1. Hepatocytes proliferation after injury, post partial hepatectomy (تجدد عن طريق خلايا الكبد)
2. The liver can replace itself (stem cells)

* Both need growth factors & cytokines and cell interactions and matrix surrounding this tissue

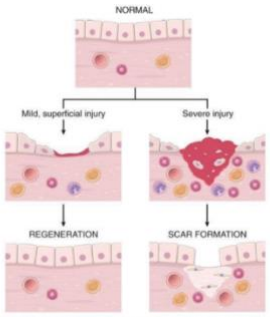


FIG. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mil...

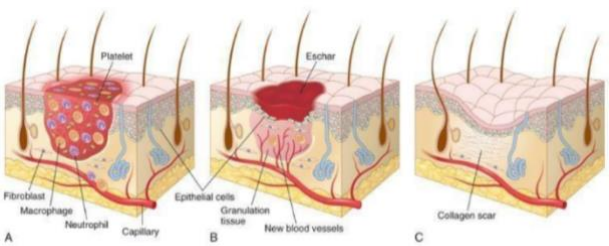


FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is ...

Repair by scarring

-Patching (prevent bleeding) > wound healing > replacing the lost tissue.
Scar formation = fibrosis = fibrous tissue = fibrous scar = scaring

Called: healing by second intention

- for severe injury (large amount of tissue loss).
- **slow**.
- repair by **scar formation**.
- The regeneration alone is not enough to fill in the gap.
-The healing requires extensive granulation tissue formation & extensive angiogenesis; to build a strong scar tissue.

-e.g: crush injury.

Steps:

1) **clot-forming**: takes minutes, forming of **hemostatic plug** that is comprised of **platelets,** to prevent further bleeding.
-Cytokines and growth factors will be released
2) **Inflammation**: takes (6-48) hours, include stimulating the macrophages (M1, M2 phases).
3) cell proliferation **(fibroblasts migration & proliferation)** that includes **angiogenesis** & **formation of granulation tissue**, takes (1-10) days.
5) **collagen synthesis.**
6) **connective tissue remodeling**: takes (2-3) weeks, up to 6 months!, it includes cleaning out the extra tissue & proteins & cell debris > formation of a strong scat tissue that is composed of a strong collagen replacing the damaged parenchyma.

Eschar: hard dry fibrin clot mostly acellular which covers the lost tissue and prevents further bleeding
*After the healing process is done, eschar will fall out and drop.

angiogenesis

- plays a central role in the process of healing by scarring.
- **Involves:** signaling pathways, growth factors, cell-cell interactions, ECM proteins, and tissue enzymes of remodeling (each step needs a special growth factors, like VEGF-A (mainly, this one involves in angiogenesis), FGF-2, & TGF-ß (the most potent fibrogenic or scar-forming mediator).
- it starts from the underneath artery.
- it is a part of initial formation of granulation tissue (fibroblasts migrate to the site of injury & proliferate, to form **granulation tissue**, then they deposit ECM proteins to form a **mature scar,** by cross-linking collagen (removing collagen type **3** and replacing it by collagen type **1** which is stronger).
- fibroblasts can differentiate into myofibroblasts (have some contractile muscle functions), to stimulate laying down more collagen to close the gap.

Steps:

1) the initial step is **Notch signaling** (sprouting/branching) (where the endothelial cells are very active, thus extend outside).
2) pericyte detachment by angiopoietin factor.
3) basement membrane degradation by metalloproteinases enzymes (MMPs).
4) ECM and growth factors interaction.
5) elongation of pericytes, basement membrane, epithelial cells, and vascular stalk.

– Enzymes for final remodeling are required to cut the extra collagen and clean up the mess after the reparative process.

*notes (from the book):

- Vascular endothelial growth factors, mainly VEGF-A, stimulate both migration & proliferation of endothelial cells, thus initiating the process of capillary sprouting in angiogenesis.
- Fibroblast growth factors, mainly FGF-2, stimulate the proliferation of endothelial cells & promote the migration of macrophages, fibroblasts, and epithelial cells to the damaged area (epithelial cells to cover epidermal wounds).
- Transforming growth factor beta (TGF-B) participate in the stabilization process, it suppresses endothelial proliferation and migration, and enhances the production of ECM proteins. (it is the most important one in our lecture ☺)

Remodeling of connective tissue

It is needed to make the scar strong and contracted.

• Cross linking of collagen (Switching type III to type I collagen), by degradation of extra collagen by Matrix Metalloproteinases (MMPs) (that are balanced by the Tissue Inhibitors of MP (TIMPs) يعني مشان ما يضلوا شغالين للأبد)

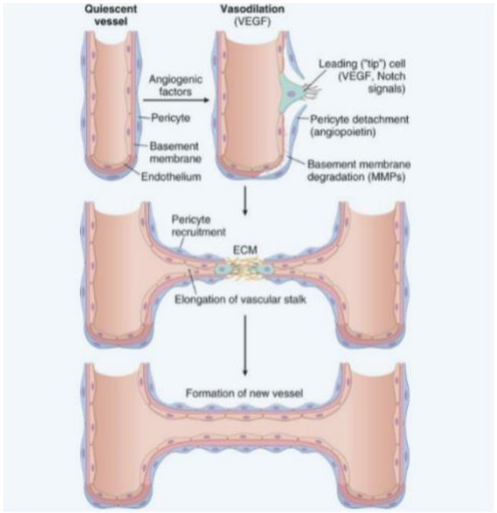
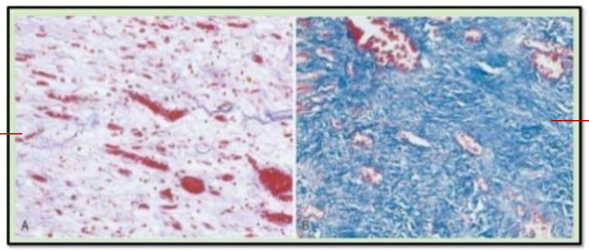


FIG. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting o...

young granulation tissue:
- H&E stain
- number of blood vessels is much more the number of mature scar tissue is very minimal
- (not strong enough)
- a blood vessel active angiogenetic process



Mature scar:
-trichrome stain
-less blood vessels, more mature scar tissue
-full of the collagen type one
-(strong)

Please refer to book summaries from the slides

FACTORS THAT IMPAIR TISSUE REPAIR

These factors impact repair speed, intensity, degree, and perfection an individual may suffer from only one or multiple **factors**

Wound Dehiscence: when a surgical incision reopens either internally or externally. sometimes because of increased intra-abdominal pressure

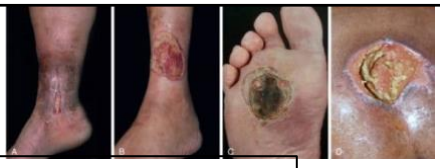
1. **Infection**: infected wound → interruption of all the reparative process → healing process will be delayed. (Antibiotics are used as an infection-avoidance in cases of *severe acute injury or *high-risk surgery or *intra-abdominal surgery)
2. **Diabetes mellitus**: (short- and long-term complications) *need extra time for healing, more support, * delay in reparative process, * negative impact on GFs & mediator's activation \\\ - *The more you control diabetes→ the more you provide proper healing.*
3. **Nutritional status:** Patients who are suffering malnutrition need parenteral nutrition before doing any surgery \\\- Proper nutrition is important for proper healing.
4. **Steroids: (strong anti-inflammatory drug)** causes delay in the reparative processes (instead of 1-2 weeks)/ cause low immunity.
   * Steroids are inhibitors in the main stem (phospholipase A2) of the arachidonic acid metabolism.
5. **Mechanical factors:** increased local pressure or torsion, Causing improper healing process & sometimes Wound Dehiscence
6. **Poor Perfusion:** due to **sever ischemia**, **atherosclerosis**, **hypertension**, **hyperlipidemia (***need more time for healing & more attention concerning their nutrients**.)**/ Antibiotics help in improving the healing process.
7. **Foreign bodies:** fragments of steel, glass, needle, medical equipment, or even bone/ Sometimes removing a foreign body from the tissue causes more damage than keeping it inside.
8. **Type and extent of tissue injury:** age , pathophysiological state
9. **Site of injury:** Ex: abdominal wounds heal slower than facial

- All injuries and wounds depend on the site of injury and the extent of the injury.

ABNORMAL HEALING

Deficientscar formation

scar is deficient and week>>serious complications; wound dehiscence.



- **Venous leg ulcers**: **superficial** and **dusky** (grey to blue)

✓ **due to** excessive venous insufficiency and stagnation of the venous system in the lower limb,

✓ **The common area**: The medial area of the lower leg

- **Arterial ulcers**: * Deep ***due to** severe ischemia in the blood supply of certain branches of an artery.

- **Diabetic ulcers "Diabetic foot"**: * Deep arterial ulcer

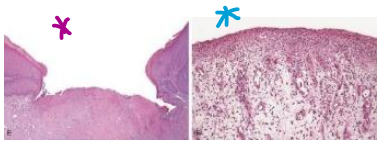
✓ in diabetic patients; **due to** peripheral neuropathy(represent gangrenes and ulcers)

- **Pressure sores/Bed ulcers**:

✓ patients with **quadriplegia** or **severe CNS illness** who stayed in the bed for a long time

pressure on an area >> ischemia >> deep ulcers

✓ The protocol followed mobilizing them every 15-30 mins (treatment is by prevention).



* Discontinuity, big deep ulcer in the squamous mucosal epithelium surface of the skin

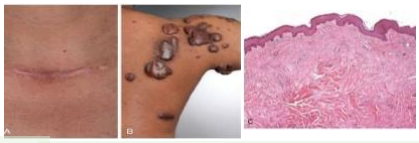
* **The floor of the ulcer:** angiogenetic granulation tissue, occurs as a response to this ulcerative morphology of the inflammatory response.

- **Wound dehiscence:**

Treatment: let it heal by granulation tissue from the bottom to the surface, [takes long time (weeks and months)]/ We have to provide antiseptic environment and protect and the wound from infection

Contractures

Excessive repair



- **Hypertrophic scar (Subcutaneous)**

✓ **Treatment**: - excision -utilizing some local anti-inflammatory medications (steroid cream>>decrease the amount of scar tissue)

***more scar formation in cases of surgery**

- **Exuberant granulation tissue (proud flesh):** Rare

- **Aggressive fibromatosis (desmoid tumor):** Subcutaneous/ deep.

- **Keloid (Subcutaneous)**

✓ A specific type of hypertrophic scar [The more you manipulate them surgically>more scars]

✓more in dark pigmented people ✓ It runs through families

cutaneous tumors→ healing by exuberant keloid material. **under the microscope:** abundant dense bundles of collagen type **I** >>squamous cell elevation

*you depend on the family history /the pigment of the patient [dark or light] to **differentiate between** keloid and hypertrophic ulcers **under the microscope**

* Can affect the function, if it involves in a joint or in an area which is sensitive for movement.

FIBROSIS OF ORGANS:

Due to: excessive deposition of collagen and ECM proteins (continuous infections or continuous immunologic injury leads to several continuous inflammations and repairs thus more formation of scar tissue, which causes organ fibrosis and loss of functions)

***TGF-ß is the most common cytokine of fibrosis.**

Diseases caused by Scar tissue formation and fibrosis

1) Liver Cirrhosis:

- the most common cause of liver cirrhosis: In the west region, is alcoholism / In our region, is chronic hepatitis C.
- Caused by severe fibrosis [almost end stage] where almost 95% of liver's tissue is replaced by fibrosis, this cause liver failure.
- Treatment: transplantation or stopping the process of fibrosis, otherwise the patient will die.

2) Idiopathic lung fibrosis: (Interstitial lung fibrosis).

- idiopathic = unknown reason.
- The whole lung will be replaced by fibrosis scar tissue, so the patient cannot breathe or utilize their lungs.
- Treatment: lung transplantation.

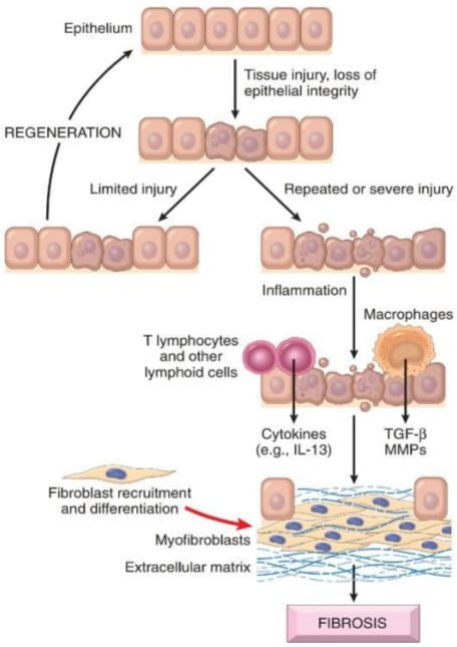
3) ESKD (end stage kidney disease): the last stage of long-term (chronic) kidney disease

- A lot of diseases that affect the kidney end up in causing severe and marked parenchymal renal fibrosis.
- patients with chronic renal disease + hypertensive nephropathy or diabetic nephropathy, may develop to ESKD.

The diagnosis of ESKD need a collaboration between both:

1- **clinicians** to follow up the history of patient to identify untreated diabetes or hypertension or glomerulonephritis [which increase the probability of ESKD]

2- **pathologists:** for looking at the renal biopsy, seeing severe fibrosis in the kidney.



From the picture:

- in small, superficial injuries: regeneration occurs quickly, and the tissue goes back to its original normal state.
- in severe tissue injury or repeated attacks of severe injury (e.g: repeated attacks of hepatitis C in the liver), this process will occur:

*inflammation and recruitment of inflammatory cells

*repair by scar formation induced by TGF-ß

*forming more fibrous tissue (instead of regeneration)

*the same cycle keeps repeating, depending on the intensity of the injury, this will lead to severe fibrosis in that organ.

liver→ liver cirrhosis

kidney→ ESKD

lung→ Idiopathic interstitial lung fibrosis

جملة عجبتني بنهاية أحد الشيتات: ""فخذ بالأسباب وكأنّها كلّ شيء، وتوكّل على الله وكأنّها لا شيء""

ادعوا لنا..
عُلا الأحدب – عائشة سلامة