

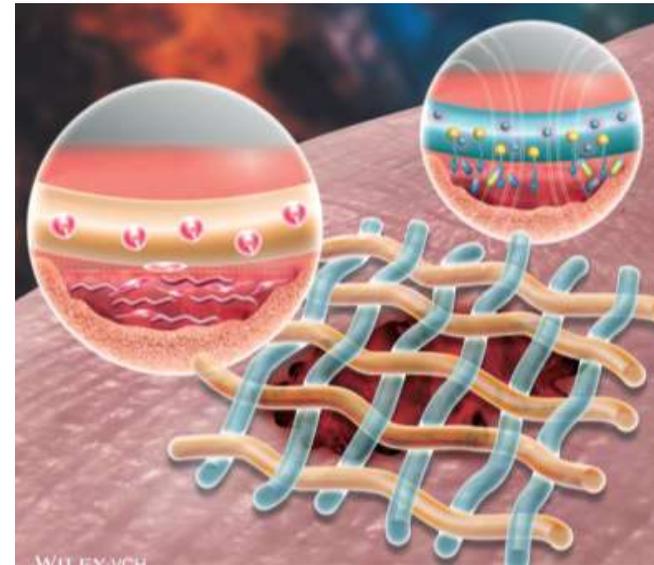


**TISSUE REPAIR**

**Hind Sarayrah, M.D.**

**19-10-2025**

- The ability of an organism to repair the damage caused by toxic insults and inflammation is critical to the survival . In fact, the inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair.



# OVERVIEW OF TISSUE REPAIR

- Repair of damaged tissues occurs by **two types of reactions**: *Depends on the type of the tissue*



تكاثر خلايا



Proliferation

قابل انه يصير له

→ regeneration

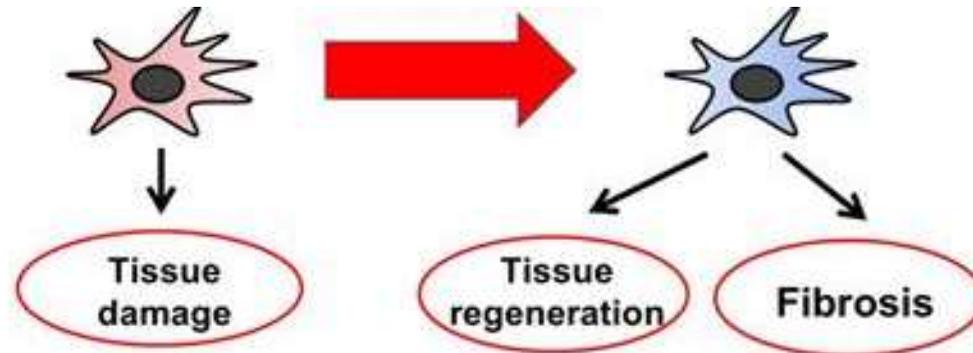
ex. Liver

غير قابل

→ scar, fibrosis

ex. nerves, muscles

- **Regeneration** by **proliferation** of residual (uninjured) cells AND **maturation of tissue stem cells**.
- **Deposition** of connective tissue to **form a scar**. /fibrosis





## 1. REGENERATION

- Proliferation of cells that survive the injury and retain the capacity to proliferate may contribute to the restoration of damaged tissues, for example:
  - In the rapidly dividing epithelia of the skin and intestines.
  - In some parenchymal organs, notably the liver.
  - Tissue stem cells.



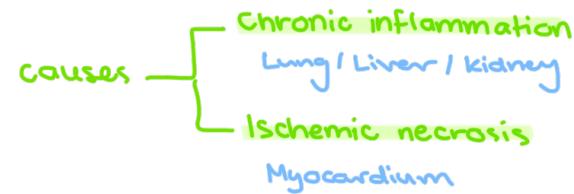


## 2. CONNECTIVE TISSUE DEPOSITION (SCAR FORMATION)

- Repair occurs by the laying down of connective (fibrous) tissue, a process that may result in formation of a scar, it occurs in:
  - injured tissues are incapable of complete restitution.
  - if the supporting structures of the tissue are severely damaged → proliferation الخلية التي تعمل بطلت قدرة تلحق

← ما عند لها القدرة إنها تعوض





## ❖ FIBROSIS Scar

- placing smth in a specific location*
- Extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction).

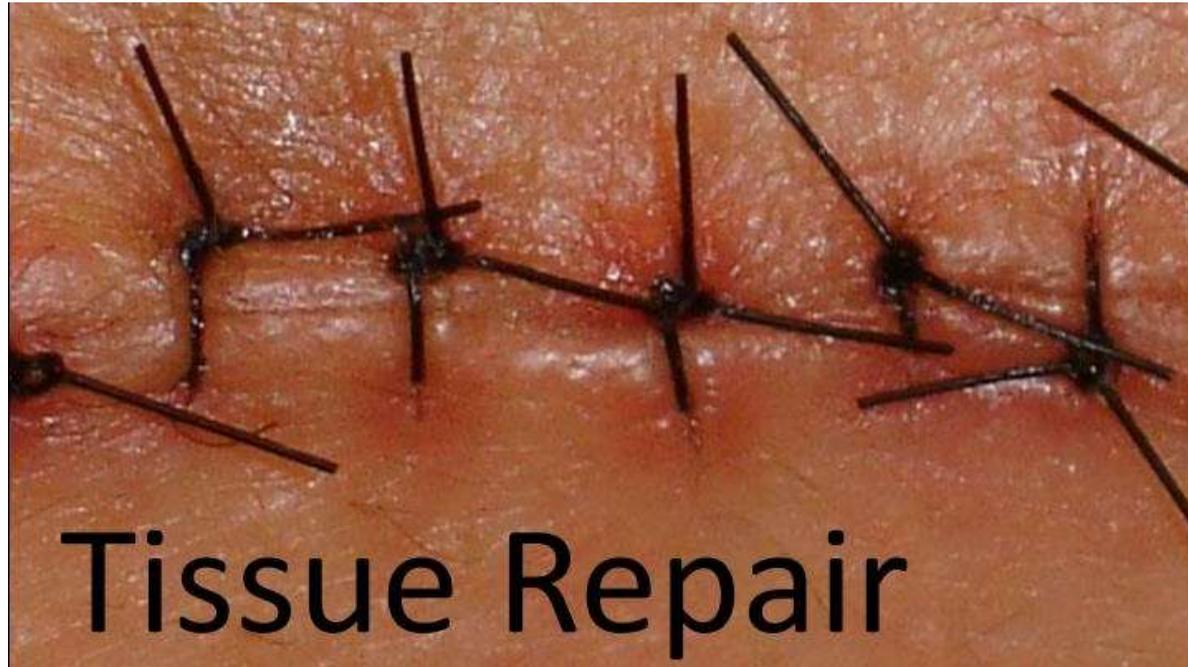
Infarction is the death of tissue due to a lack of blood supply and oxygen

➤ Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function. ✓✓



- The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity.

قدرة الخلايا نفسها (بدون أي عوامل خارجية) إنها تنقسم وتتجدد من تلقاء نفسها



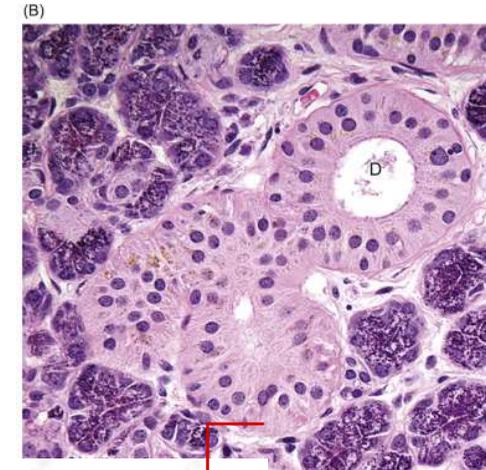
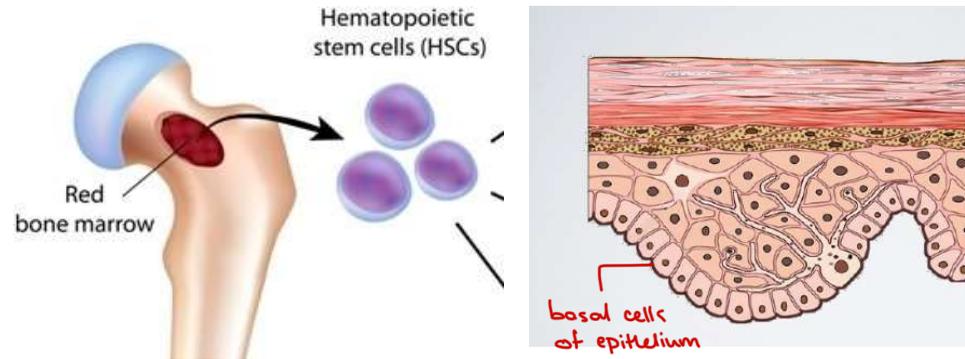
# Tissue Repair



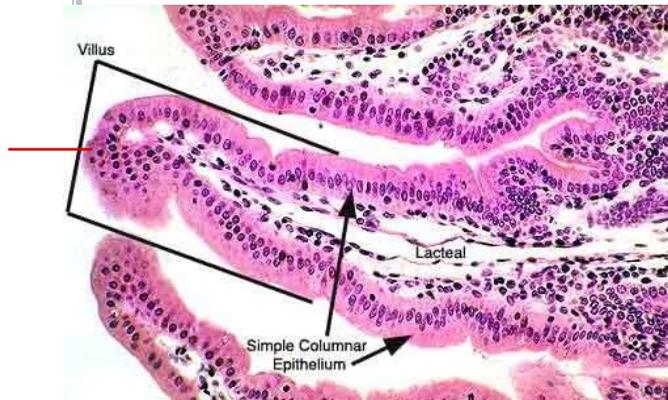
➤ **1. labile tissues** have high proliferative capacity  
cells are constantly being lost and must be continually replaced by new cells that are derived from tissue stem cells and rapidly proliferating immature progenitors.



Ex: epithelium, intestine, bone marrow, RBCs, WBCs



Columnar cell lining GIT tract (Intestine)



Transitional epithelium lining the ureter + bladder

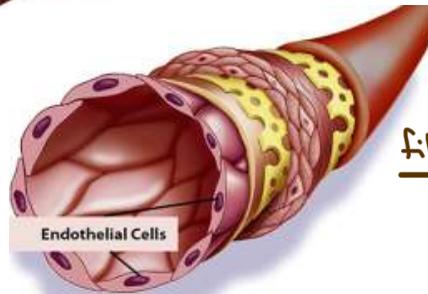
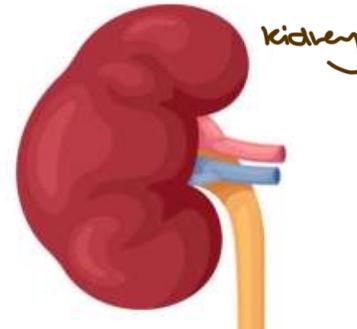
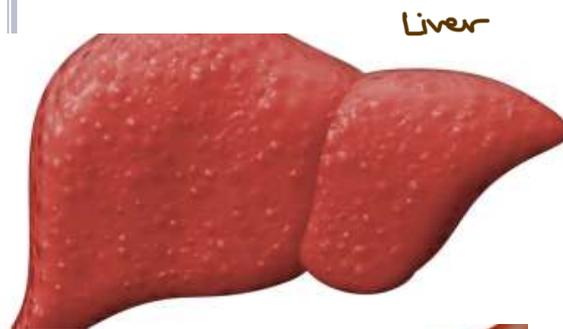


- 2. stable tissues

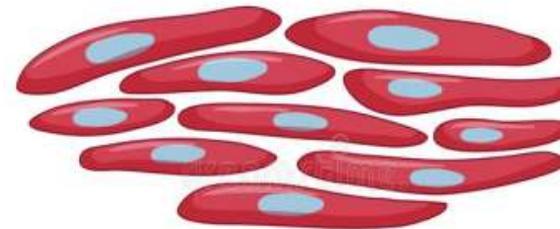
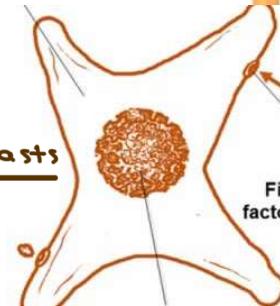
- are made up of cells that are normally in the **G0** → Stable stage of the cell cycle and hence not proliferating, but they are capable of dividing in response to injury or loss of tissue mass.

الأغلة  
مهمة

بالحالات الطبيعية ما بتكاثروا، بس لو صار في إصابة عندهم قابلية أنهم بيدؤوا proliferation



fibroblasts



→ Smooth muscle cells

ما عندهم قابلية أبدًا إنهم يتكاثروا ويعوضوا مكان الإصابة ، فبصير مكان الإصابة scar



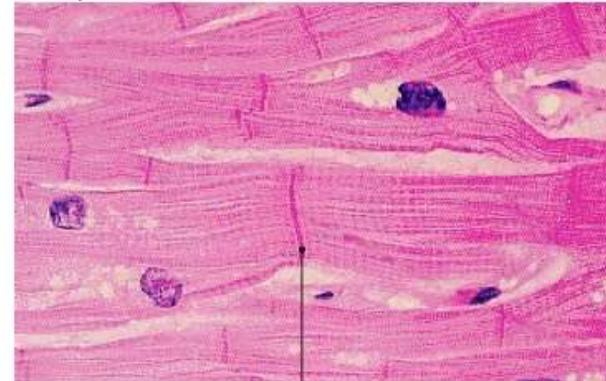
### ➤ 3. PERMANENT TISSUES

- consist of terminally differentiated **nonproliferative cells**, such as the majority of **neurons** and **cardiac muscle cells**.
- Injury to these tissues is **irreversible** and results in a **scar**, because the **cells cannot regenerate**.

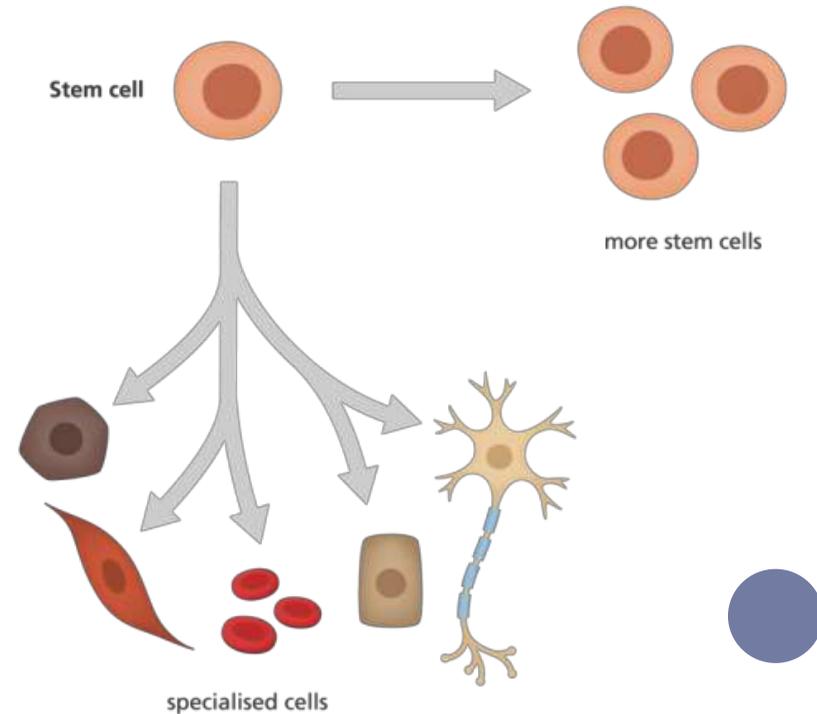


+

عضلة القلب



- ❖ In the process of regeneration, proliferation of residual cells is supplemented by development of mature cells from stem cells



## ❖ **LIVER** REGENERATION

- The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy,

يعني حتى لو انشال جزء منه (زي في عملية اسمها partial hepatectomy, لما يشيلوا جزء من الكبد), الجزء اللي باقي ينمو ويعوّض المفقود

- Regeneration of the liver occurs by **two major mechanisms**:

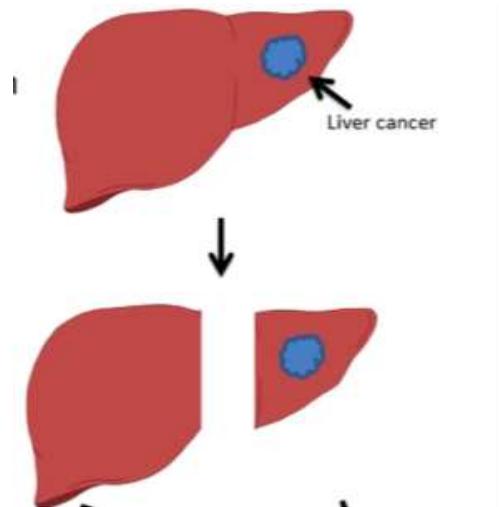
- **proliferation of remaining hepatocytes.** → intrinsic proliferative capacity
- repopulation from **progenitor cells.**

في بعض الحالات (لما الخلايا الكبدية العادية تتعب أو تتضرر كثير وما تقدر تنقسم) يجي دور الخلايا الجذعية الموجودة في الكبد، تقدر تتحول لخلايا كبدية جديدة



- Restoration of normal tissue architecture can occur only if the residual tissue is **structurally intact**.
- if the **entire tissue is damaged**, regeneration is **incomplete** and is accompanied by scarring.

إذا تلف الإطار كليًا ← تجديد ناقص ومعه (scarring) ← تجديد كامل



partial surgical resection



liver abscess

○ 1. Proliferation of hepatocytes following partial hepatectomy.

- In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes.

حتى لو شالوا 90% من الكبد  
الـ 10% الباقية بتقدر بالتكاثر ترجع الكبد تقريباً لحجمه الطبيعي ووظيفته

- This process is driven by مى بحفز الخلايا انها تبرا بالتكاثر؟

- cytokines such as IL-6 produced by Kupffer cells, → Macrophages of the liver  
➤ hepatocyte growth factor (HGF) produced by many cell types.

بتجهز خلايا الكبد للاستقبال الـ growth factor  
بانه قلبي الخلايا تجهز receptors له على سطحهم.

$G_0 \rightarrow G_1$



- 2.Liver regeneration from progenitor cells.
  - In situations in which the proliferative capacity of hepatocytes is impaired, progenitor cells in the liver contribute to repopulation, such as:
    - after chronic liver injury.
    - inflammation.
- بهاي الظروف بترا الـ  
progenitor cell  
تستغل وتكاشر





## REPAIR BY SCARRING Fibrosis

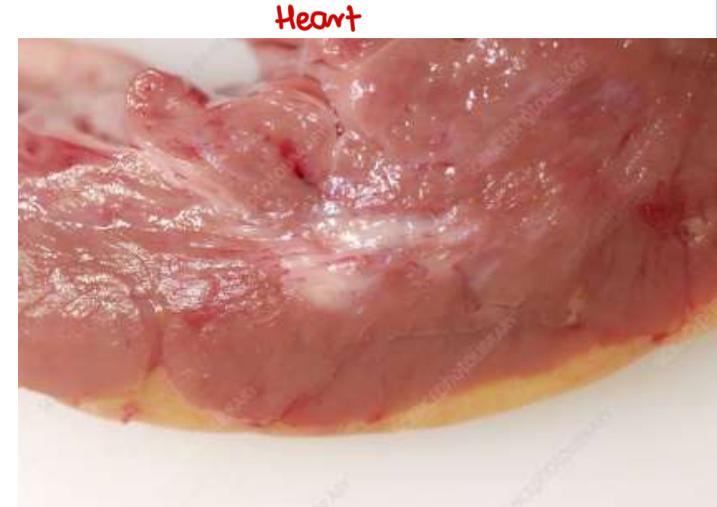
- if repair cannot be accomplished by regeneration alone, it occurs by:
  - ❖ replacement of the injured cells with connective tissue, leading to the formation of a scar,
  - ❖ or by a combination of regeneration of some residual cells and scar formation.

هاي العملية بتحافظ على شكل العضو ، بس  
خلص بكون هذا الجزء فقد وظيفته الأصلية لأنه  
صار CT بدل الخلايا الأصلية

خليط بين تجدد وتنذب



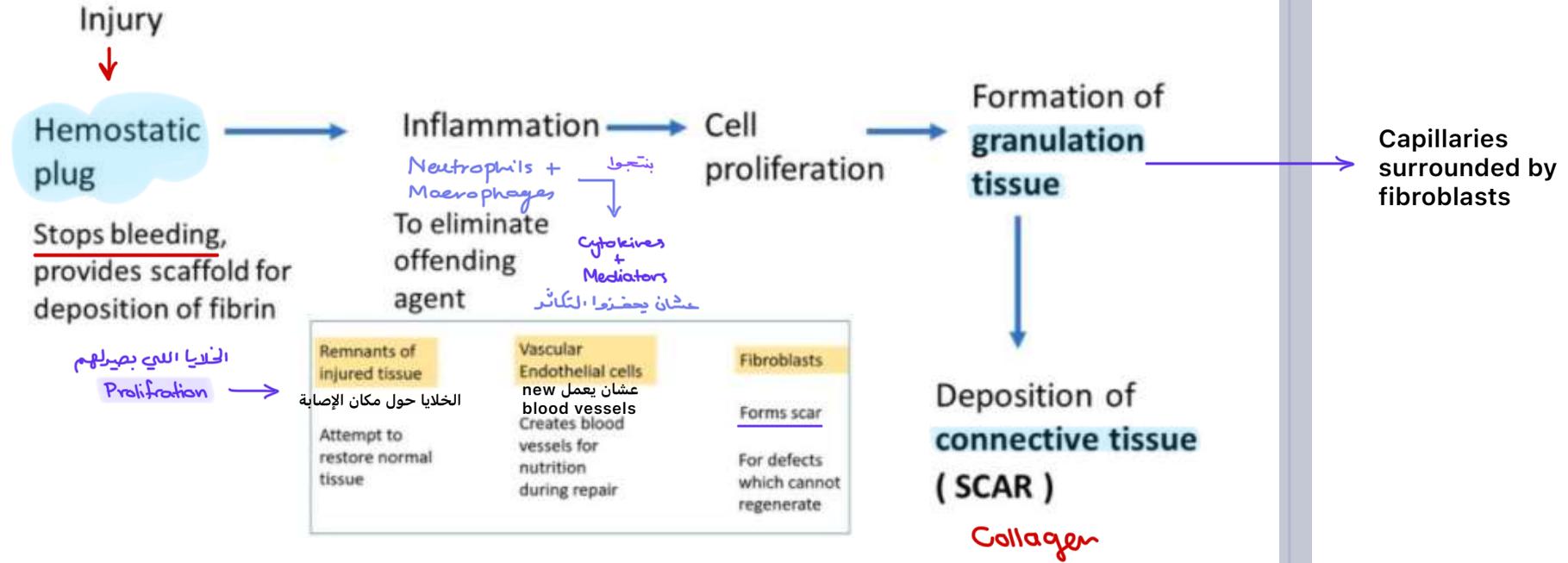
- The term **scar** is most used in connection to **wound healing in the skin**.
- Replacement of parenchymal cells in any tissue **by collagen**, as in the heart after myocardial infarction.



عاجل بنسبها Scar  
علاجها ال اخلية بنسبها Fibrosis  
(الاشي نفس الشي بالضبط بس اختلاف مسميات)

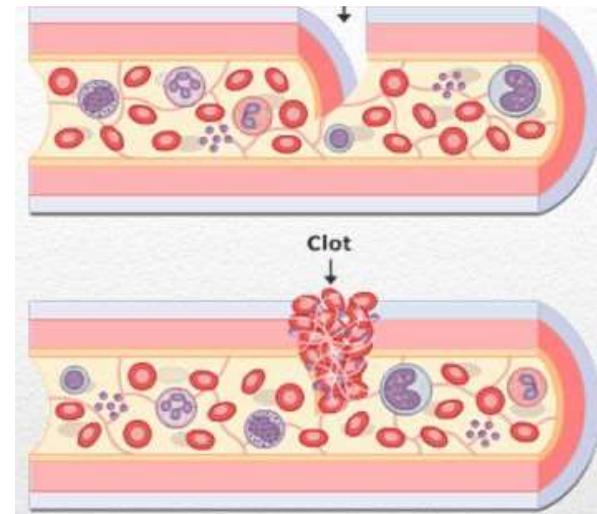


## Steps in Scar formation

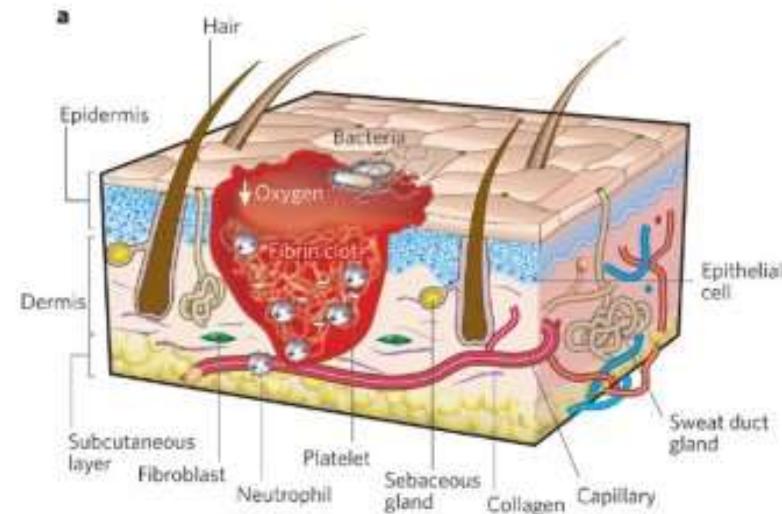


## STEPS IN SCAR FORMATION

- 1. Within minutes after injury, a hemostatic plug comprised of platelets is formed:
  - ❖ stops bleeding .
  - ❖ provides a scaffold for infiltrating inflammatory cells.



- 2. Inflammation:
  - Include acute and chronic inflammatory responses.
  - The inflammatory cells:
    - eliminate the offending agents
    - clear the debris



أهم خلية بالعملية



- Macrophages are the central cellular players in the repair process:
  - **M1** macrophages :
    - clear microbes and necrotic tissue and promote inflammation .
  - **M2** macrophages: *Have a look at slide 36*
    - produce growth factors that stimulate the proliferation of many cell types in the next stage of repair.

M1 → تنظيف وتحفيز الالتهاب

M2 → نمو وتجديد وإصلاح





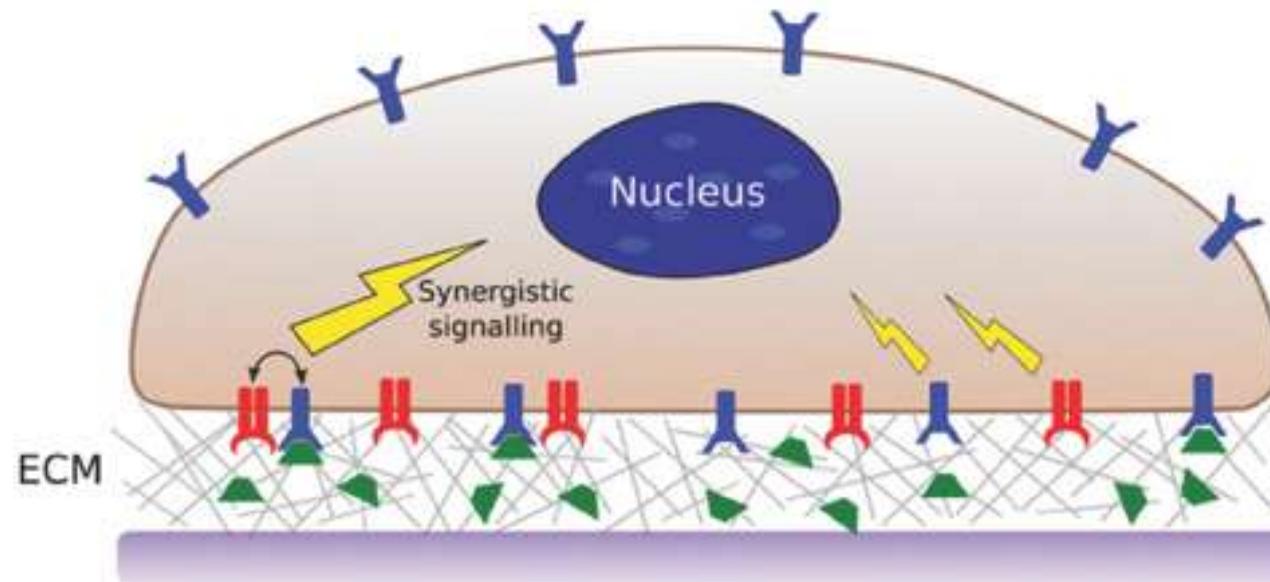
- 3. Cell proliferation.
- In the next stage, which takes up to **10 days**, several cell types migrate to close the now-clean wound, including :
  - Epithelial cells: migrate **over the wound to cover it.**
  - Endothelial and other vascular cells: proliferate to **form new blood vessels**, a process known as angiogenesis
  - Fibroblasts: proliferate and migrate into the site of injury and **lay down collagen fibers** that **form the scar.**

توصل الأوكسجين والغذاء للخلايا اللي  
قاعدة تبني النسيج الجديد

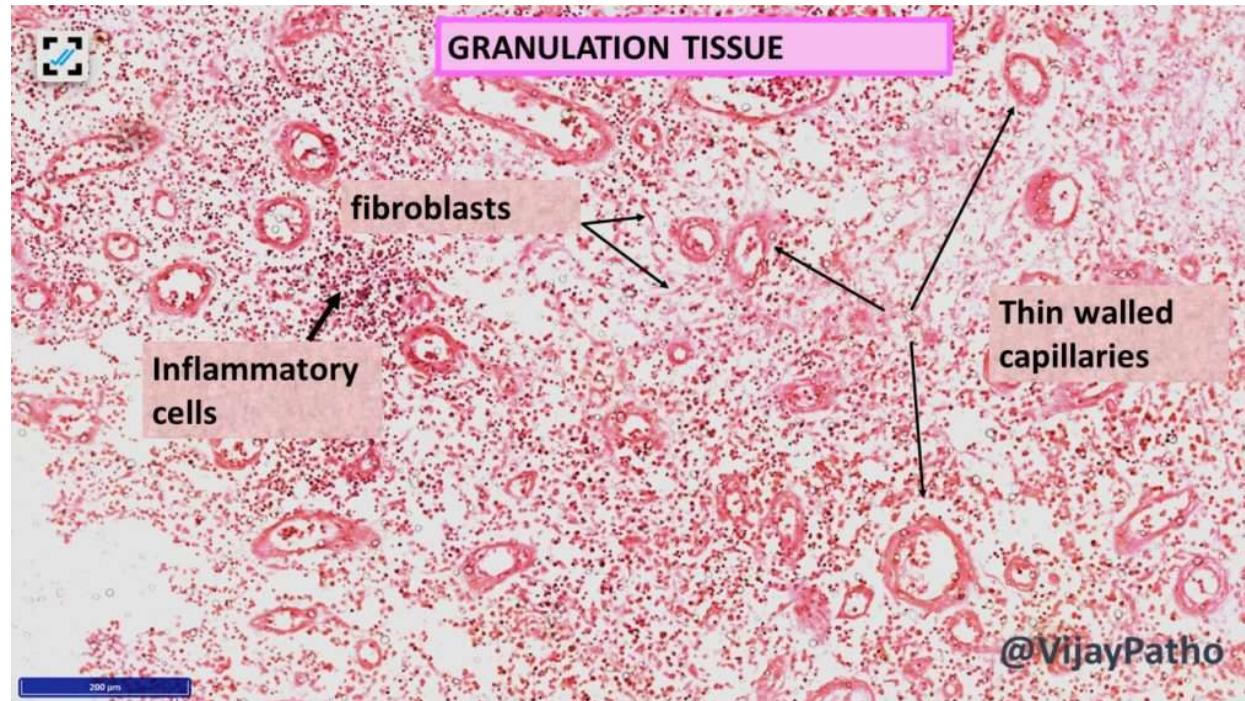
تغطي Endothelial cells  
تبني شبكة دم جديدة Endothelial / Vascular  
تفرش الكولاجين اللي بيكوّن الندبة Fibroblasts



- ❖ Cell proliferation is driven by signals provided by growth factors and from the extracellular matrix.



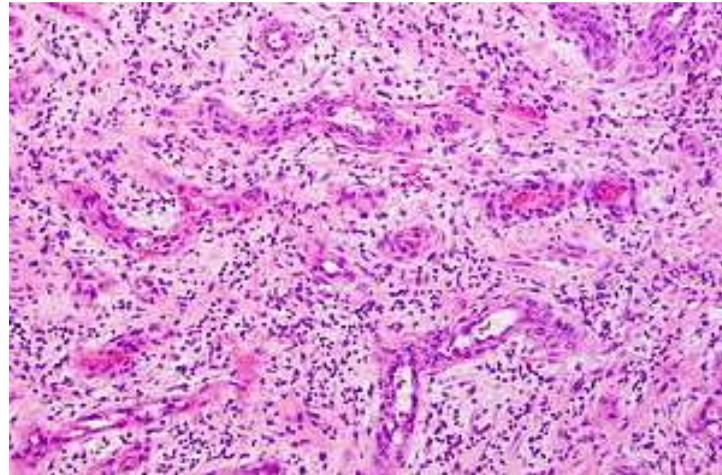
- The combination of proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells, forms a **granulation tissue**. *Important*





## Granulation tissue.

pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.



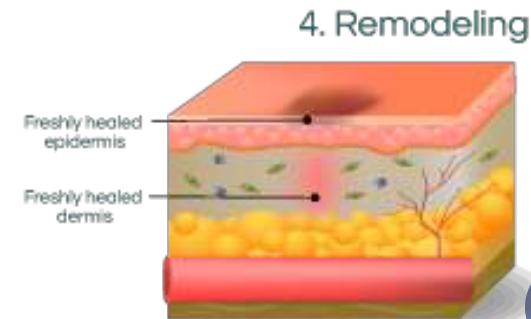
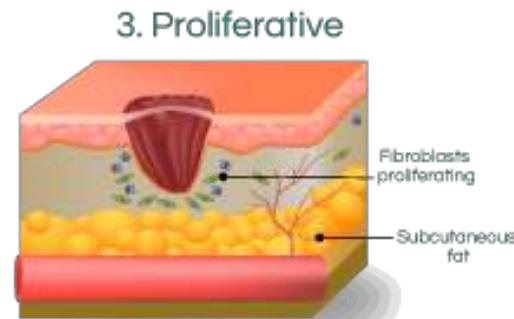
proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells



## 4. REMODELING.

الـ connective tissue اللي أنتجته الـ fibroblasts يبدأ يتنظّم ويتقوى الكولاجين يُعاد ترتيبه (reorganized) بطريقة منظمة أكثر، فيتحوّل من نسيج إسفنجي ولين إلى scar

- The connective tissue that has been deposited by fibroblasts is reorganized to produce the stable fibrous scar.
- This process begins 2 to 3 weeks after injury and may continue for months or years



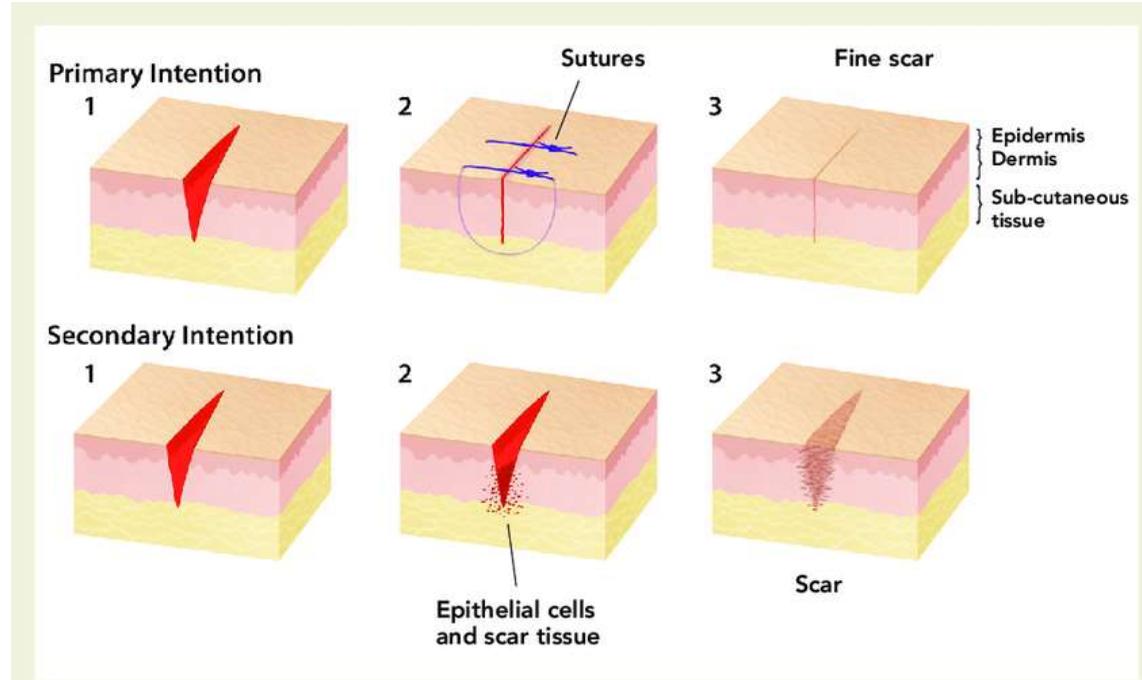
- Healing of skin wounds can be classified into healing by :

↔ first intention (primary union).

↔ second intention (secondary union).

يحصل في الجروح الصغيرة والنظيفة الي أطرافها قريبة من بعض (زي جرح جراحي بخياطة).  
بصير التئام سريع، كمية الـ scar قليلة جدًا لأن الخلايا الطلائية بتغطي الجرح بسرعة.

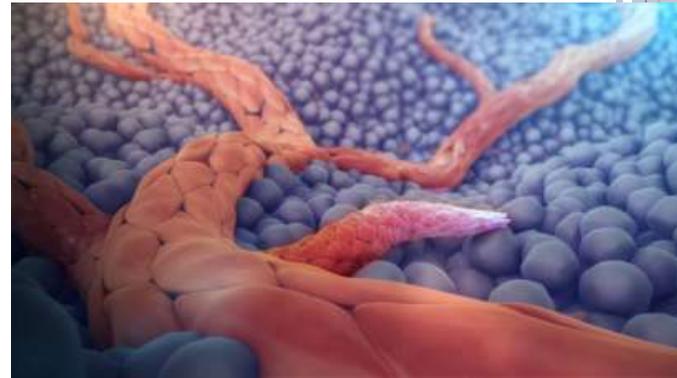
بصير في الجروح الكبيرة أو المفتوحة (الي فيها فقد كبير أو التهاب).  
بحتاج granulation tissue أكثر، و fibrosis أكثر يعني ندبة أكبر وتحتاج وقت أطول للشفاء.



## ANGIOGENESIS

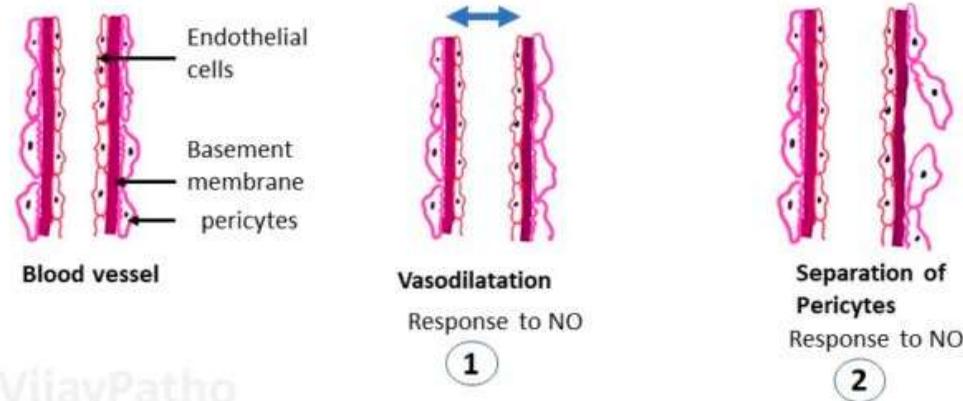
- Angiogenesis is the process of new blood vessel development from existing vessels.
- It is critical in:
  - healing at sites of injury.
  - development of collateral circulations at sites of ischemia.
  - allowing tumors to increase in size

بتستغل العملية  
عشان تتغذى وتكبر



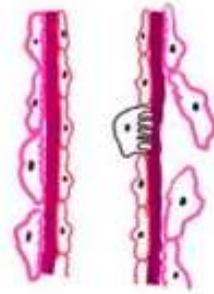
- **Angiogenesis** involves **sprouting of new vessels from existing ones**, and consists of the following **steps**:
- **Vasodilation** in response to NO and increased permeability induced by VEGF .  
 Vascular Endothelial Growth Factor
- **Separation of pericytes** from the abluminal surface to allow formation of a vessel sprout .

الأوعية تتوسع عشان الدم يمر بسهولة.  
 الجدار يصبح أكثر نفاذية VEGF يهيئ المنطقة للخلايا الجديدة.  
 ال pericytes تتحرك ، يسمح لبداية تكوين فرع جديد من الوعاء.

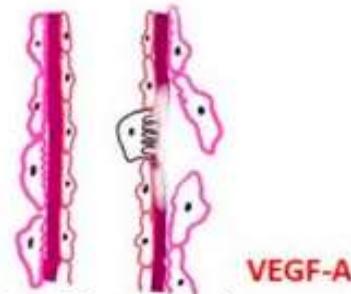


- **Migration** of endothelial cells toward the area of tissue injury.
- **Proliferation** of endothelial cells just behind the leading front (“tip”) of migrating cells.

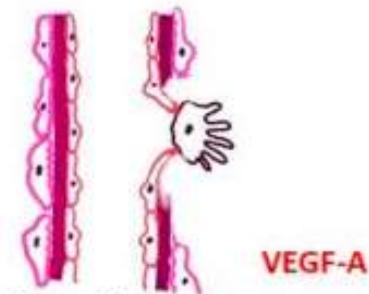
tip cells ← الخلايا تتحرك  
 الخلايا خلفهم تتكاثر ← تمديد الوعاء



Tip cell formation  
 3



Breakdown of the basement membrane  
 4



Formation of a vessel sprout  
 5

@VivavPatho



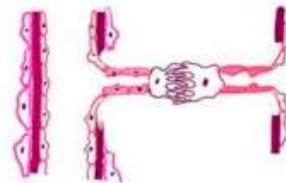
- Remodeling into capillary tubes.

استرخاد

- Recruitment of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel.

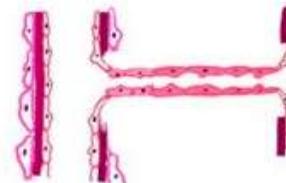
Stopping

- Suppression of endothelial proliferation and migration and deposition of the basement membrane



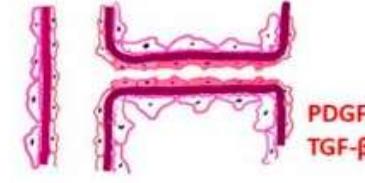
Fusion of tip cells

9



Remodeling into capillary tubes

10



Recruitment of periendothelial cells/pericytes and basement membrane deposition

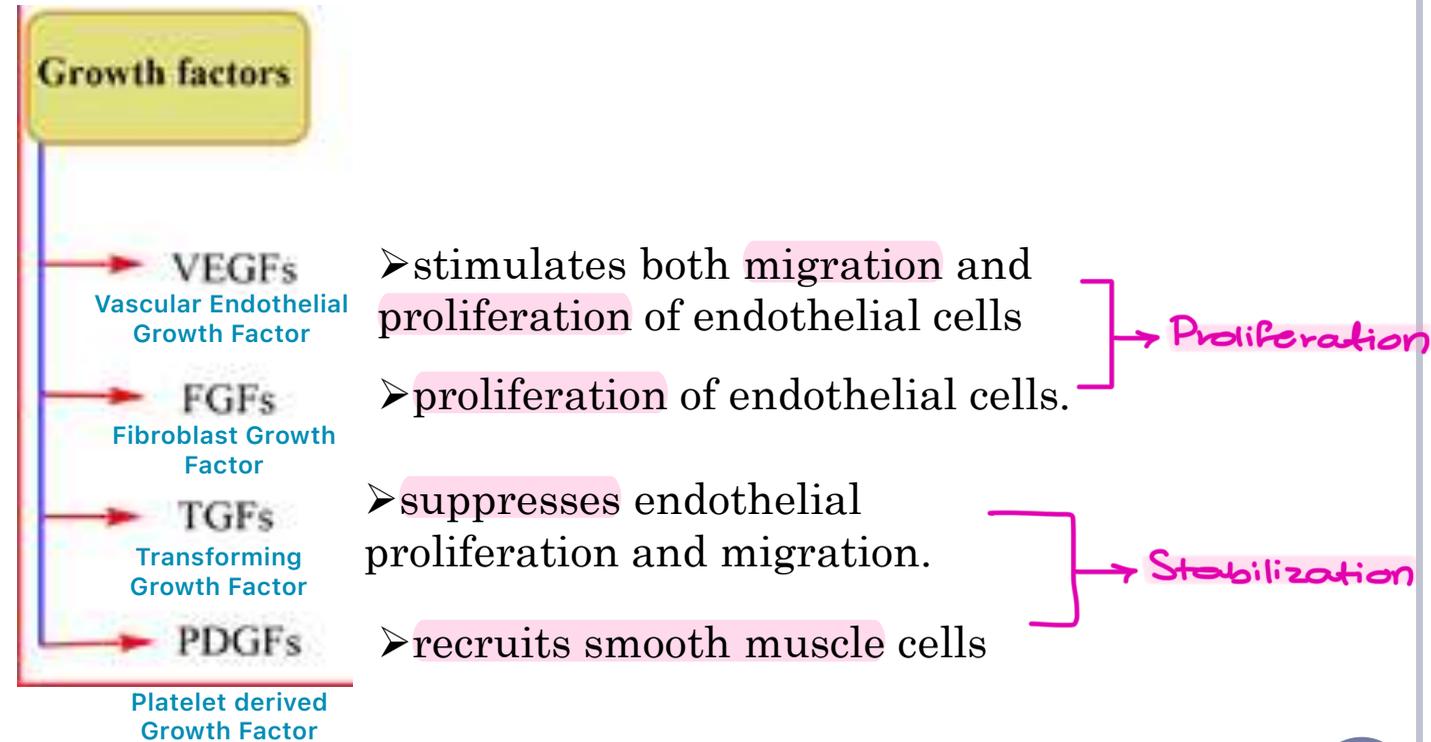
11

ترتيبها ← أنابيب دقيقة  
 استدعاء الخلايا الداعمة ← تثبيت الوعاء  
 التثبيت النهائي ← basement membrane



The process of **angiogenesis** involves several **signaling pathways**, cell-cell interactions, ECM proteins, and tissue enzymes:

### 1. Growth factors:



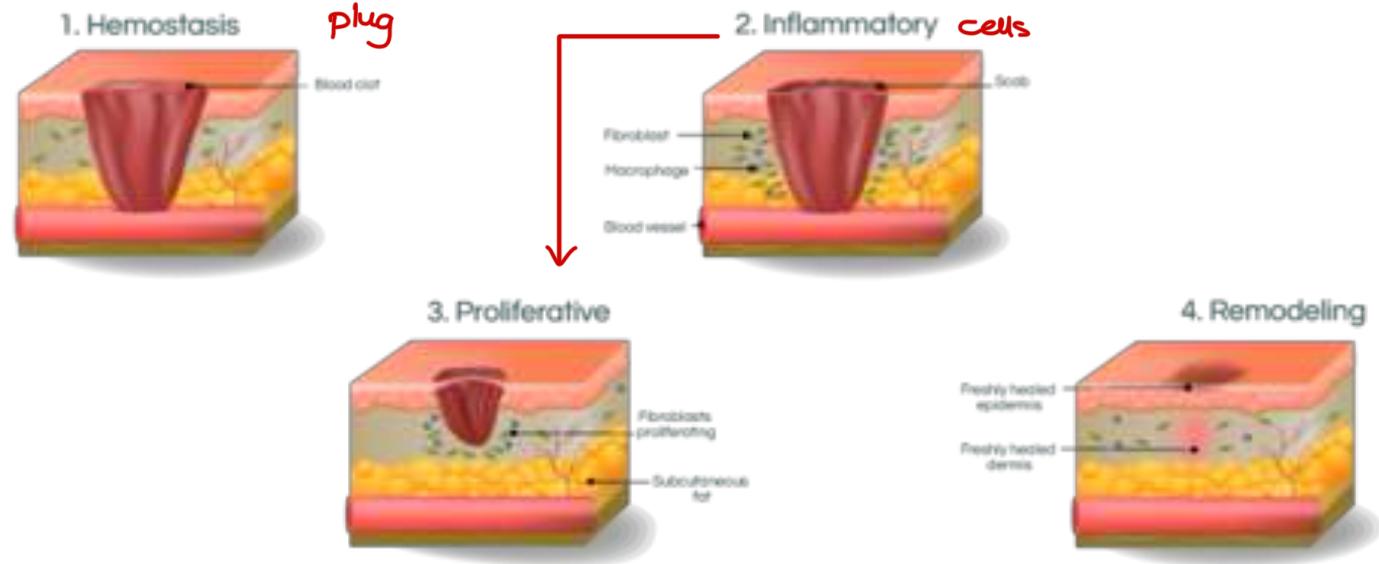
❖ So PDGF and TGF-B participate in the stabilization process

- 2. Notch signaling. الموجّه اللي يوجّه نمو الأوعية ويحدد شكل الشبكة
- regulates the sprouting and branching of new vessels .
  
- 3. ECM proteins:
- participate in the process of vessel sprouting in angiogenesis, through interactions with integrin receptors .
- Enzymes in the ECM, notably the matrix metalloproteinases (MMPs), degrade the ECM to permit remodeling and extension of the vascular tube.

Matrix metalloproteinases (MMPs)  
تحلل جزء من الـ ECM  
الهدف: إفساح المجال للخلايا (endothelial)  
لتشكيل الأوعية وتمديدها



# 4 STAGES OF WOUND HEALING



### 3. PROLIFERATIVE PHASE :

#### PROLIFERATION OF FIBROBLASTS

- The laying down of connective tissue occurs in two steps:
  - (1) migration and proliferation of fibroblasts into the site of injury.
  - (2) deposition of ECM proteins produced by these cells

↓  
Collagen

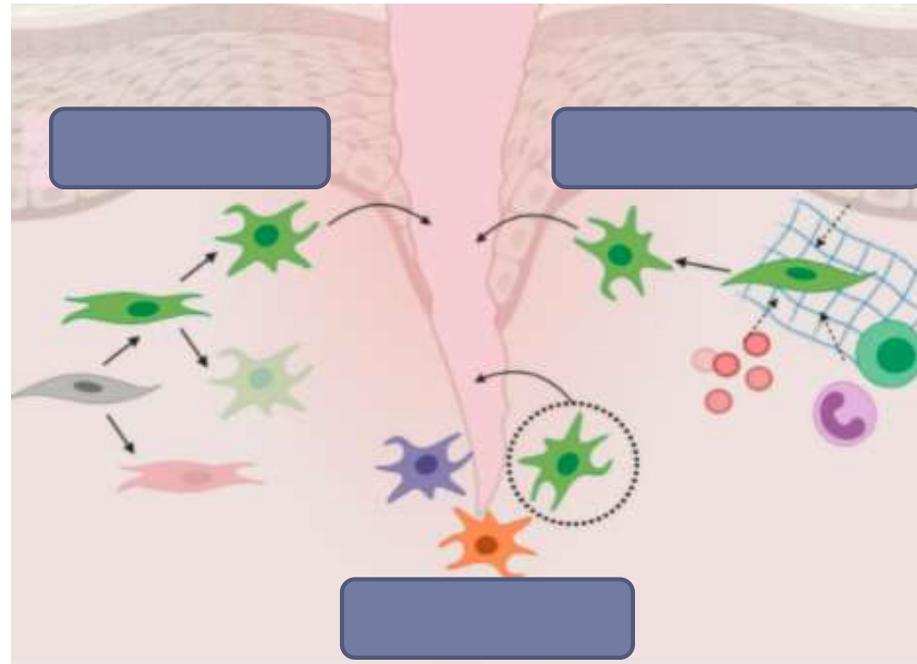


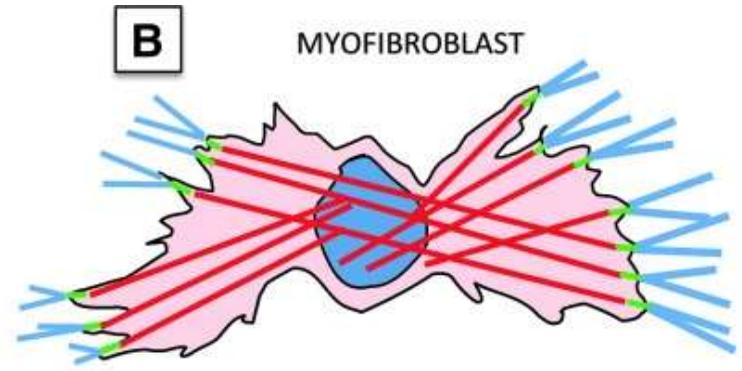
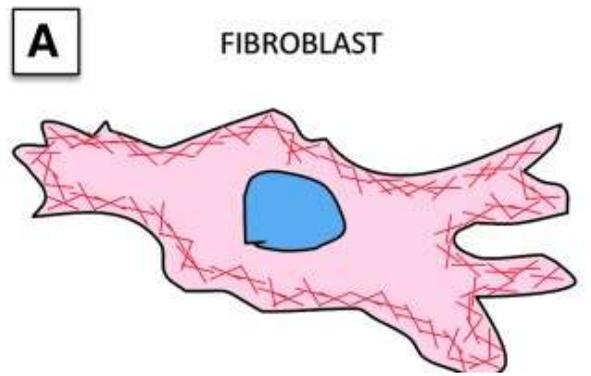
- These processes are under the control of cytokines and growth factors, including:
  - PDGF.  
PDGF (Platelet-Derived Growth Factor)
  - FGF-2.  
FGF-2 (Fibroblast Growth Factor-2)
  - TGF- $\beta$ .  
TGF- $\beta$  (Transforming Growth Factor Beta)
- The major sources of these factors are alternatively activated (M2) macrophages



- In response to cytokines and growth factors.
- fibroblasts enter the wound.
- fibroblasts vs myofibroblasts?
- Activated fibroblasts and myofibroblasts produce collagen.

Fibroblasts: الخلايا الأساسية التي تنتج الكولاجين والبروتينات الأخرى للـ ECM.  
 Myofibroblasts: نسخة متحركة وقادرة على الانقباض تساعد على شد الجرح وتقليص حجمه

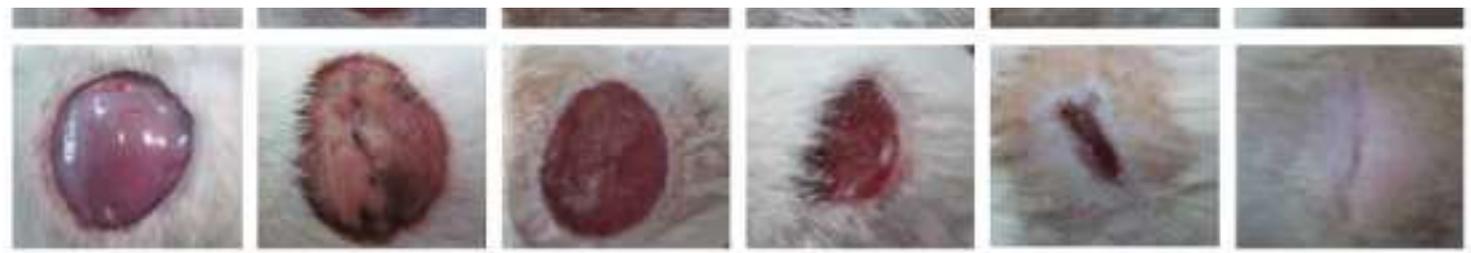




have Actin filaments



Contracting





## ❖ TGF- $\beta$ Transforming Growth Factor

- The most important cytokine for the synthesis and deposition of connective tissue proteins.
- It is produced mainly by alternatively activated macrophages. M2
- TGF- $\beta$  act to:
  - stimulates fibroblast migration and proliferation.
  - increases the synthesis of collagen and fibronectin.
  - decreases the degradation of ECM by inhibiting metalloproteinases.

ينقل fibroblasts للجرح  
يحفز إنتاج الكولاجين والفيبرونيكتين  
يمنع تكسير النسيج ← يضمن أن الندبة  
تصير قوية وثابتة

تحلل جزء من الـ ECM  
الهدف: إفساح المجال



- As healing progresses, the number of proliferating fibroblasts and new vessels decreases.   
مع الوقت:  
- تقل الخلايا والأوعية  
- Fibroblasts  
تركز على الكولاجين
- fibroblasts progressively assume a more synthetic phenotype and increased collagen synthesis. 
- Collagen synthesis by fibroblasts begins early in wound healing (days 3–5) and continues for several weeks, depending on the size of the wound.
- scar maturation :
  - transformation of the highly vascularized granulation tissue into a pale, largely avascular scar due to progressive vascular regression.



## 4. REMODELING OF CONNECTIVE TISSUE

- process of wound matrix breakdown by matrix metalloproteinases and synthesis of new ECM

metalloproteinases (MMPs): القديم ECM تكسر جزء من  
Fibroblasts: جديد ECM تنتج

- Aimed to increase scar strength.

- Wound strength increases because of:

➤ cross-linking of collagen.  $\uparrow$  التشابك  $\rightarrow$  يعني قوة أكبر

➤ increased size of collagen fibers

➤ shift of the type of collagen deposited, from type III collagen early in repair to more stable type I collagen.

from type 3 to type 1 (stronger)





❖ In well-sutured skin wounds, strength may recover to 70% to 80% of normal skin by 3 months.



metalloproteinases

Tissue Inhibitors of Metalloproteinases

# A balance of MMPs and TIMPs regulates the size and nature of the scar

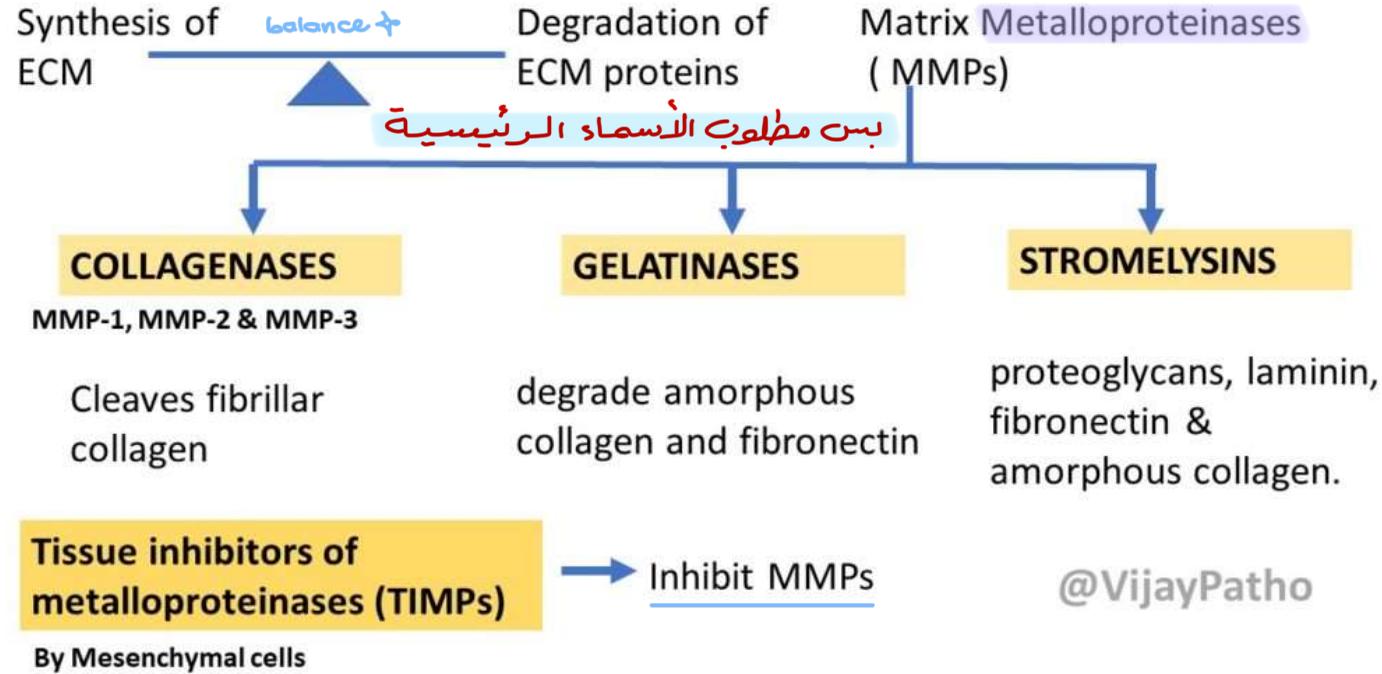
تكسير الـ ECM

يمنع نشاط الـ

فجيرة في توازن

لو زاد الأول بتكون الندبة ضعيفة بسبب تكسير النسيج  
لو زاد الثاني بتكون الندبة سميكة زيادة عن اللزوم

## REMODELING OF CONNECTIVE TISSUE



@VijayPatho

تعديل النسيج وإعادة تنظيمه  
↑

إنزيمات تحلل مكونات الـ Extracellular matrix

## MATRIX METALLOPROTEINASES (MMPs).

- they are calcium-dependent zinc containing endopeptidases.  $Ca^{2+} + Zn$
- They are capable of degrading all kinds of extracellular matrix proteins.
- produced by a variety of cell types (fibroblasts, macrophages, neutrophils).



# FACTORS THAT IMPAIR TISSUE REPAIR

عوامل تقيق العملية





healing and repair ما ال  
 ما بصير زي المفروض ...  
 بصير ulcer بدل ال scar

# ABNORMALITIES IN TISSUE REPAIR

Defects in Healing  
 الجرح ما يلتئم صح

Excessive cell proliferation  
 تكاثر خلايا مفرط  
 الجسم overreacting

Excessive scarring  
 الندبة سميبكة ومشوهة

**WOUND DEHISCENCE**  
 الجرح انفتح !  
 (زي لما تنفك الخيوط)

**CHRONIC WOUNDS**  
 مزمنة, ليش؟  
 Venous ulcers  
 بسبب ضعف تدفق الدم الوريدي  
 Arterial ulcers  
 بسبب نقص التروية  
 Diabetic ulcers  
 نتيجة ضعف التئام الجروح عند مرضى السكري  
 Pressure sores  
 من الضغط الطويل عالجرح

**EXUBERANT GRANULATION**  
**EXCESSIVE FIBROBLAST PROLIFERATION**  
 Desmoids

**HYPERTROPHIC SCAR**  
**KELOID**  
**CONTRACTURE**





# I. DEFECTS IN HEALING: CHRONIC WOUNDS

ما تلتئم بشكل طبيعي أو تحتاج فترة طويلة جدًا حتى تشفى

- 1. Venous leg ulcers:
  - Varicose
  - Heart failure
- Seen in elderly people as a result of chronic venous hypertension, which may be caused by severe varicose veins or congestive heart failure.  
دوالي فشل في القلب (احتقائي)
- These ulcers fail to heal because of poor delivery of oxygen to the site of the ulcer.

بسبب ضعف الدورة الدموية الوريدية، ما بوصل أكسجين كفاية للمنطقة المصابة فبالتالي الجرح ما يلتئم



## 2. Arterial ulcers:



- develop in individuals with **atherosclerosis** of peripheral arteries, especially associated with **diabetes**.

لما الشرايين تتضيّق بسبب التصلّب، الدم ما يوصل كفاية للأنسجة فيصير نقص أكسجين وبالتالي الجروح ما بتلتئم بسهولة.  
تقرحات

## 3. Pressure sores :

- are areas of skin ulceration and necrosis of underlying tissues. الضغط المستمر يمنع تدفق الدم الطبيعي ← يصير نقص أكسجين (ischemia) ← تموت الخلايا ← تتكوّن قرحة.
- caused by **prolonged compression of tissues against a bone**, for example, in **bedridden**. The lesions are caused by mechanical pressure and local ischemia.



المرضى المبردين للفراش





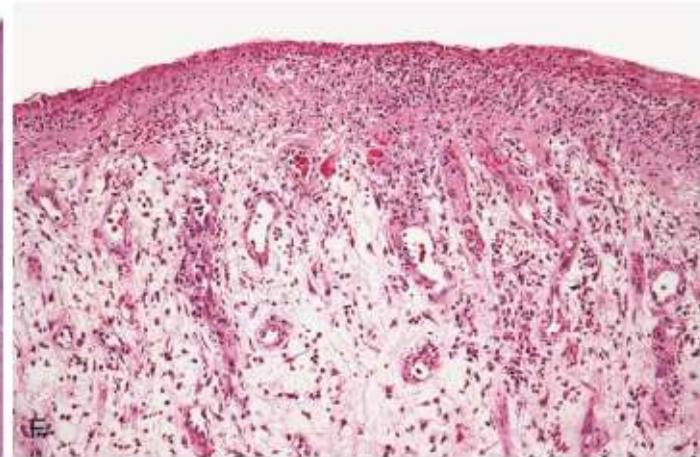
4. Diabetic ulcers; caused by { Ischemia  
Neuropathy  
Infections

الأطراف السفلية  
(القدمين)

○ affect the lower extremities, particularly the feet. Tissue necrosis and failure to heal are the result of small vessel disease causing ischemia, neuropathy, systemic metabolic abnormalities, and secondary infections.

السكري يسبب تلف الأعصاب،  
فالمريض ما يحس بالجرح أصلاً  
ويمكن هذا الجرح يتورث وتبدأ  
عدوى ثانوية secondary infection





epithelial ulceration and extensive granulation tissue in the underlying dermis



انفتاح الجرح بعد ما تسكر

## 5. wound rupture (dehiscence):

- occurs most frequently after abdominal surgery and is a result of increased abdominal pressure, such as may occur with vomiting, coughing, or ileus. تجمع غازات
- More in obesity, malnutrition, vit. C deficiency.

لأن كلهم يضعفوا تكوين الكولاجين وبالتالي تقل قوة الالتئام





## II EXCESSIVE SCARRING

- ✓ The accumulation of **excessive amounts of collagen** may result in a raised scar known as a **HYPERTROPHIC SCAR**.  
الجسم يحاول يصلح الجرح، لكن بدل ما يوقف وقت الكفاية، يكمل بإفراط وينتج كمية كبيرة من الكولاجين فيصير شكل الجرح مرتفع ومتيبس ولكننننن تبقى بحدود الجرح نفسه ما بتنتشر حولينه (عكس الكلويد keloid)
- ✓ These often grow rapidly and **contain abundant myofibroblasts**.
- ✓ develop after **thermal or traumatic injury** that **involves the deep layers of the dermis**.  
*burns*
- ✓ they tend to **regress over several months**.





Not beyond the boundaries  
ما يتطلع عن حدود الجرح



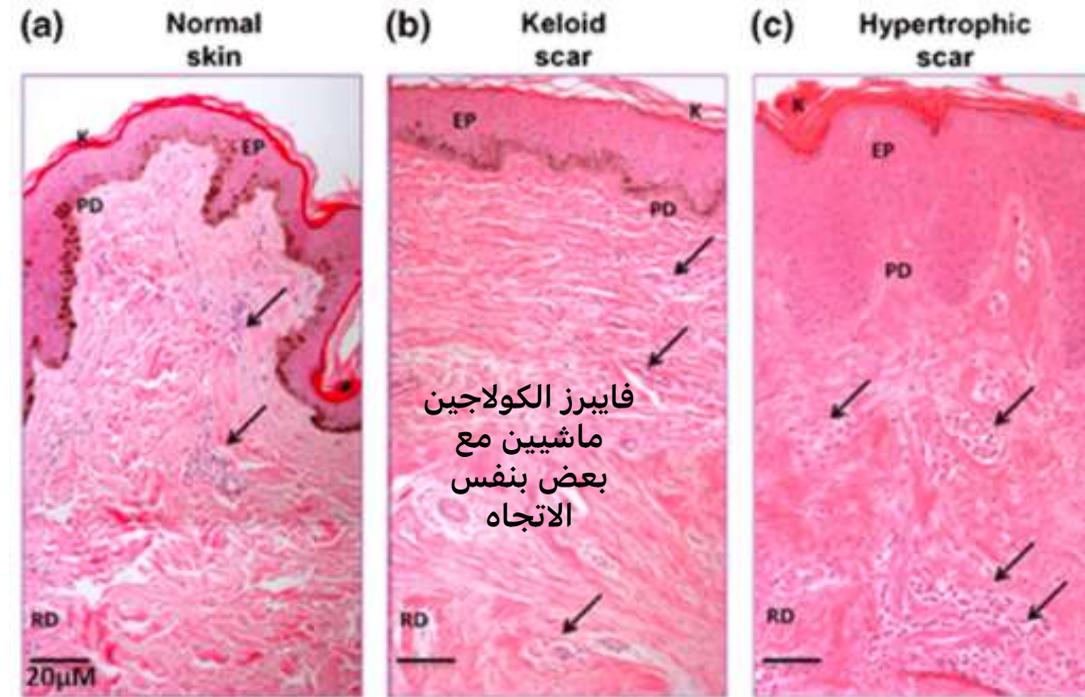


- **KELOID:**

يعني النسيج الزائد يمتد للجلد الطبيعي حوالين الجرح

- It is a hypertrophic scar that grows beyond the boundaries of the original wound and does not regress.





- A. In normal skin, the characteristic **random orientation** and bundle formation of collagen fibres
- B. increased number of **thick collagen** fibres **arranged in bundles**
- C. The collagen fibres were **arranged randomly** and showed **highly cellular zones**

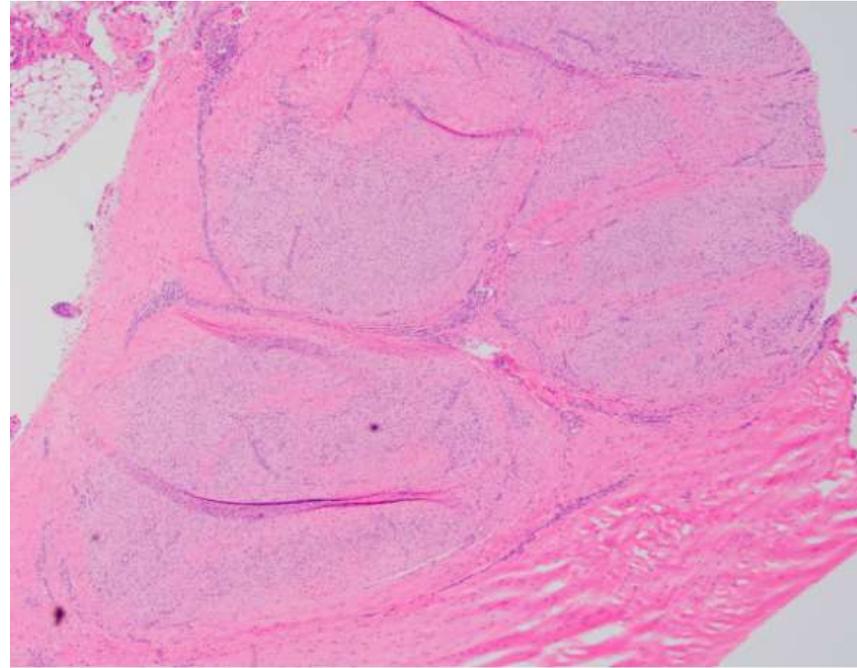
يحصل لما الأنسجة اللي عادة تكون مرنة مثل العضلات أو الأوتار تتحول إلى نسيج صلب (fibrosis) بسبب الحروق العميقة غالبًا فيفقدوا مرونتهم وقدرتهم عالحرقة بسهولة



## CONTRACTURE

- permanent shortening of a muscle or joint develop when normally elastic tissues such as muscles or tendons are replaced by inelastic tissues (fibrosis).
- prone to develop on the palms, the soles, and the anterior aspect of the thorax.
- Contractures are commonly seen after serious burns and can compromise the movement of joints.





**Nodule formation:**

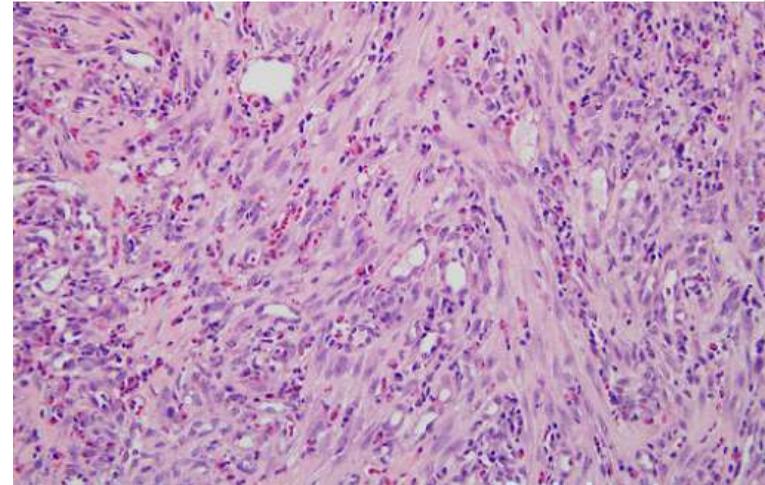
Composed of spindle cells (myofibroblasts and fibroblasts)  
with dense collagen.





### III EXCESSIVE CELL PROLIFERATION

- **Exuberant granulation** Overgrowth of granulation tissue
- formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks reepithelialization .



## FIBROSIS IN PARENCHYMAL ORGANS

- excessive deposition of collagen and other ECM components in a tissue.

طبيعية pathologic  
○ scar vs fibrosis????

- **Fibrosis** is a **pathologic process** induced by **persistent injurious stimuli** such as chronic infections and immunologic reactions, and is typically **associated with loss of tissue**.
- It may be responsible for substantial organ **dysfunction** and even **organ failure**. !



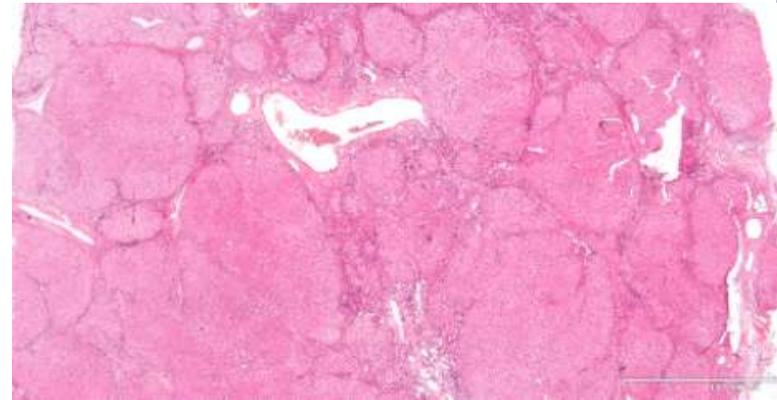
# EXAMPLES OF FIBROTIC DISORDERS



- 1. liver cirrhosis. *fibrosis in the Liver* تليف الكبد



Nodules

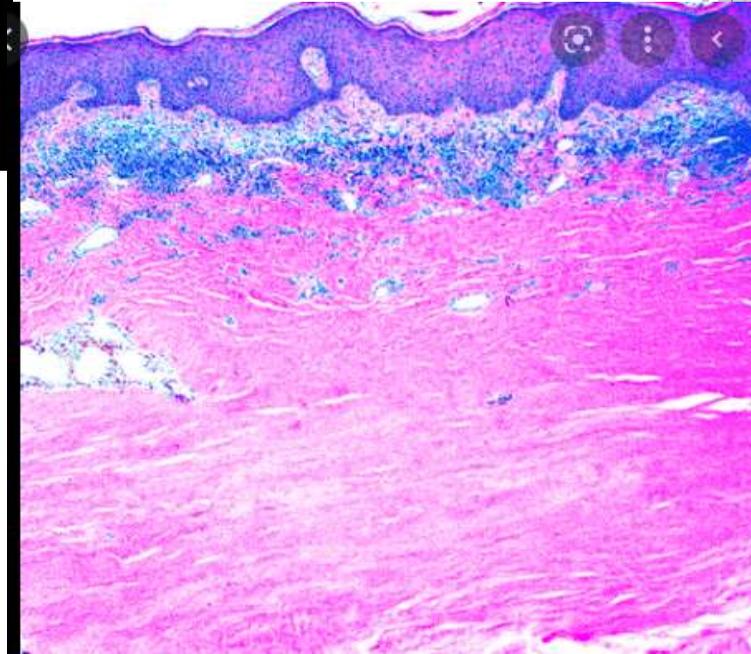


## 2. SYSTEMIC SCLEROSIS (SCLERODERMA).



### تصلب الجلد

الجهاز المناعي يحفز الجسم على إنتاج  
كولاجين زائد في الجلد وبعض الأعضاء  
الداخلية



### 3. END-STAGE KIDNEY DISEASE.

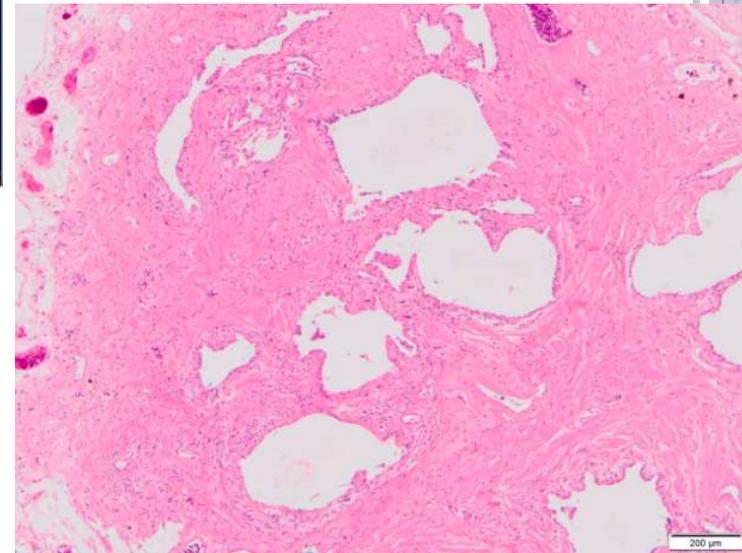
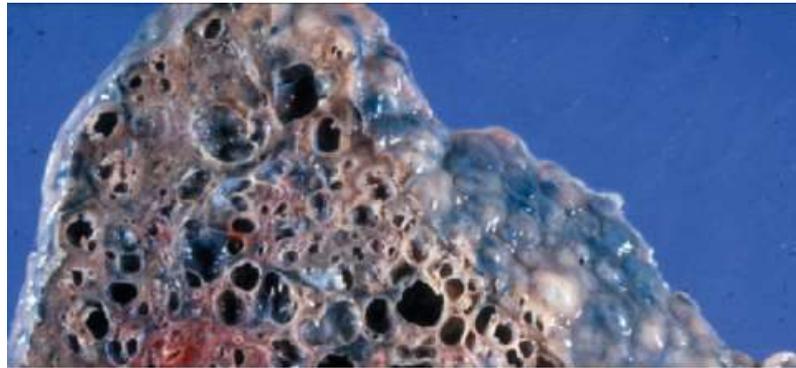


كل هاي الأمراض عندها نفس المشكلة الأساسية:  
النسيج الطبيعي يتحول إلى نسيج صلب  
(fibrosis) بسبب إصابة مستمرة  
العضو يفقد وظيفته تدريجيًا



❖ fibrosing diseases of the lung.

Grossly: Honeycomb, Cystic spaces with fibrotic wall  
Histology: cystic spaces lined by bronchiolar epithelium and fibrotic wall



خلية النخل

جدران صلبة

