

Pathology (tumor) lec 7

Healing by repair (scar formation and fibrosis)

1. When a **mild injury** occurs in a tissue with a good power of replication, the damage cells can be totally replaced by exactly similar cells (regeneration).

Ex: fracture bone , superficial skin wound.

لما بتحصل اصابة بسيطة مش عميقة زي (كسر العظام او جرح سطحي في الجلد) الخلايا المتضررة في النسيج ده ممكن تستبدل كلها بخلايا تانية من نفس النوع وبكدة يكون حصل regeneration

2. When **severe injury** affects parenchymal and stromal tissue with marked tissue loss and damage to large number of stem cells, the injured tissue cant regenerate and fibrosis occurs.

3. If the damage is still in progress inflammation becomes chronic leading to stimulation of ECM deposition and fibrosis.

4. In the past 2 steps, healing by **repair** occurs with combination of regeneration and fibrosis with scar formation.

**التوضيح:

- لو حصل قطع في الجلد ال epidermal tissue of the skin بيكون مكون من labile cells ويحصله **regeneration** healing by .

- والجزء الباقي (اللي مش بيتكون من labile cells) بيحصله **fibrosis** healing by **and scar formation** .

- في ال healing by repair النسيج اللي حصل فيه خلل بنصلحه بنوع تاني من الانسجة (مش من نفس النوع) .

➤ Steps of healing by repair :

1. **Inflammation** to remove damage tissues.
2. Formation of new blood vessels (**angiogenesis**).
3. **Proliferation** of parenchymal and connective tissue cell (fibroblast).
4. Synthesis and deposition of extracellular matrix proteins (**scar**).
5. Connective tissue **remodeling** . (to prevent over growth of granulation tissue)

**للتوضيح:

- في ال healing by repair يحصل التالي:
- بيتكون ال granulation tissue اللي هي عبارة عن highly vascular inflammatory cells + fibroblasts+ blood من connective tissue مكون من . capillaries
- بعدين لما الدم يتسحب شوية من المنطقة بتحصل ال fibrosis .
- ولما الدم يتسحب تماما بتتكون ال scar .

❖ Angiogenesis in repair process:

- **Definition:** formation of new blood vessels by branching from pre-existing vessels.

يعني تكوين او عية دموية جديدة من او عية دموية كانت موجودة قبل كدة

- **Mechanism:**

- during wound healing, angiogenic capillary sprouts invade the fibrin/fibronectin – rich wound clot , and within a few days organize into a microvascular network throughout the granulation tissue.

اثناء التئام الجرح, براعم الشعيرات الدموية بتبدا تغزو ال fibrin-rich wound clot (ودي بتبقى عبارة عن الطبقة اللي بتتكون لما الجلد بيبدأ يلم) بعدها الشعيرات دي بتكون شبكة في ال granulation tissue .

- As collagen accumulates in the granulation tissue to produce scar, the density of blood vessels decrease.

❖ **Importance of angiogenesis in repair process:**

1. Normal process of growth and development.
2. Formation of granulation tissue.
3. Vascularization of ischemic tissue.

❖ **Steps of angiogenesis:**

1. Nitric oxide causes **vasodilatation** of pre-existing blood vessels.
2. Vascular endothelial growth factor (VEGF) causes **increased permeability**.
3. Metalloproteinase degrades the basement membrane.
4. Plasminogen activator disrupts endothelial cells contact.

5. Endothelial cells **proliferate and migrate** towards angiogenic stimulus.
6. Endothelial cells **maturation** into capillaries tube.
7. Peri-endothelial cells (pericytes and vascular smooth muscle) **recruitment**.

❖ Phases of wound healing:

1. **Inflammatory phase:** inflammatory cells recruitment.
2. **Proliferation phase:** migration and expansion of parenchymal cells (re-epithelialization) , endothelial cells (angiogenesis) and connective tissue cells.
3. **Maturation phase:** ECM deposition and remodeling with wound contraction.

❖ Types of wound healing:

Healing by first intention (primary union)	Healing by second intention (secondary union)
Occurs in: clean cut wounds as surgical incision and knife cuts. بيحصل مثلا في القطع الجراحي والجرح بالسكينة	Occurs in: septic wounds, ulcers, abscesses and burns. بيحصل في الجروح العميقة , القرحة , الخراج والحروق
1. Minimal cell death	1. Marked cell death
2. Minimal basement membrane damage	2. Marked basement membrane damage

<p>Edges of the wound: closely approximated by suture.</p> <p>حواف النوع دة من الجروح ممكن تقربها من بعض تاني بالخيطة</p>	<p>Edges of the wound: they aren't in contact (wide gap is present)</p> <p>حواف النوع دة من الجروح زي في حالة الحرق مثلا مينفعش نعالجها بالخيطة</p>
No foreign bodies or infection	Foreign bodies or infection may be present
<p>Ends with: 1. Formation of minimal fibrosis.</p> <p>2. good re-epithelialization</p> <p>(minimal scar)</p>	<p>Ends with: 1. Formation of dense fibrosis.</p> <p>2.greater angiogenesis.</p> <p>3.abundant collagen deposition</p> <p>(dense scar)</p>
No scar contracture	Significant scar contracture
<p>**contracture: over contraction</p> <p>يعني الجلد يلم وينكمش اوي</p>	
Complications are rare	Complications are common
امكانية حدوث مضاعفات نادرة	شائعة

❖ Steps of wound healing:

1. **Formation of blood clot:** (تجمع دموي او جلطة)

- It acts to stop bleeding. عشان توقف النزيف.
- A matrix rich in **growth factors** and **cytokines**.
- A matrix for migrating **leukocytes** and **stromal cells**.

d) Leukocytes start phagocytosis and remove necrotic debris.

2. Formation of granulation tissue:

a) Its formed of proliferating **fibroblasts** and **endothelial cells**.

b) Its **highly vascular** loose connective tissue.

c) Blood vessels leak protein and fluid causing tissue **edema**.

السوائل بتخرج برة الاوعية الدموية وبتسبب edema يعني تجمع السوائل في النسيج

d) Granulation tissue is a framework for scar formation (**young scar**).

3. Cell proliferation and collagen deposition:

a) Invading leukocytes are replaced by **macrophages**.

b) Macrophages : 1- remove necrotic debris.

2- help angiogenesis.

3- deposit ECM by their growth factors.

c) Granulation tissue is converted into **scar** composed of fibroblasts and collagen.

d) TGF- β (transforming growth factor) is the most important stimulant for fibroblasts proliferation.

TGF- β عامل مسؤول عن نمو وتكوين ال fibroblasts

4. Scar formation:

- a) More collagen deposition.
- b) **Decrease** number of blood vessels.
- c) Formation of **avascular scar**.
- d) Intact epithelium covering.

ال scar يتبقى مكونة من fibroblasts and collagen ويتبقى avascular يعني
مفياش او عية دموية

5-Wound contraction :

- it occurs mostly in large wounds .
- The cause is myofibroblasts and smooth muscle cells.
- It may cause **reduced scar and deformity (contracture)**

(ممكن الجرح يفضل يصغر و يشد جامد و يسبب الم جامد)

6-Connective tissue remodeling :

-Extracellular matrix (ECM) deposition and remodeling by matrix **metalloproteinases (MMPs)** .

N.B: MMPs is responsible for degeneration of extra formed collagen .

-MMPs require **Zinc** for proper action .

-MMPs is inhibited by **TGF-B** .

7-Recovery of tensile strength (tensile stretch of collagen) :

-its completed after 3 months .

-its due to increase **collagen deposition** .

➤ **Complications of wound healing** : (ممكن يجي مقالي ف الفاينال و لازم نكتب كل النقط)

1) **Infection** : especially in people suffer from **bacteremia** (لو عملوا عملية و) and in **diabetic** patients due to : (الأدوات كانت ملوثة)

*decrease function of leukocytes and macrophages .

*increase virulence of microorganisms in a high glucose environment .

*increase adherence of microorganisms to diabetic cells .

2) **Inadequate granulation tissue formation leads to ulceration** .

(ال granulation tissue ممكن ما يتكونش كويس و يحصل خطأ فيه ف بيتحول ل ulcer)

3) **Keloid formation (proud flesh)** : excessive formation of granulation tissue that produces a hypertrophic scar covered by thin epidermis , its due to **overdone repair** .



4) **Wound contracture** : its reduction in size of the scar due to excessive contraction , it's a complication of **extensive burn** and may lead to wound deformity .

5) **Weak scar** : in the anterior abdominal wall may lead to incisional **hernia** (الفتاء)

(فيه بعض الناس بيكون عندهم ضعف في abdominal muscle و ف حالة لم عملوا عملية مثلا و تكونت scar كنتيجة لل healing عادي هيحصل protrusion للعضلة الضعيفة و تفضل تخبط في ال scar مع كل مجهود المريض هيعمله و دا هيسبب الم)

6)Traumatic neuroma (amputation neuroma) : which is a painful mass formed of **proliferated nerve cells** .

(تجمعات خلايا عصبية شبيهة ال benign tumor تحصل في حالة قطع عصب معين)

7)Fistula (فتحة للخارج) and sinus (فتحة بين منطقتين مجوفتين) : a tract between two body cavities or cavity to outside , they may complicate surgical wounds .

➤ Factors affecting wound healing (delayed healing) :

- 1) Ischemia (نقص وصول الدم لمكان معين)
- 2) Infection , large size wound and foreign body .
- 3) Ionizing radiation .
- 4) Protein malnutrition (نقص البروتين في التغذية) and vitamin C and zinc deficiency (scurvy)
- 5) Old age .
- 6) Diabetes mellitus .
- 7) Glucocorticoids therapy (cortisone) : which causes atrophy so it used in keloid scar treatment .

(بما ان ادوية الكورتيزون بتبطأ نمو الانسجة ف بتستخدم لعلاج ال keloid scar)

✚ Bone healing ::

➤ Steps of bone healing :

- 1)the healing of a fracture occurs by **regeneration** (*because bone is formed of stable cells*)
- 2)The fractured bone should be put in **proper position** .
- 3) the gap between the fractured ends is filled with **hematoma** with **polymorphs ,macrophages , fibroblasts and new blood vessels** .

4) Platelets and inflammatory cells release **PDGF , TGF-B , FGF and interleukins** that stimulate **osteoprogenitor cells , osteoclasts and osteoblasts** .

5) The osteoclasts , polymorphs and macrophages will **phagocytose** and remove any fragments of bone blood clots and debris .

6) This is followed by formation of **osteoid tissue** by osteoblasts , this osteoid tissue consists of **collagen , osteoblasts and little amount of calcium** , *osteoblasts secrete alkaline phosphatase leading to more calcification (mineralization)* .

7) the osteoid tissue is arranged in three layers named (**calli**) :

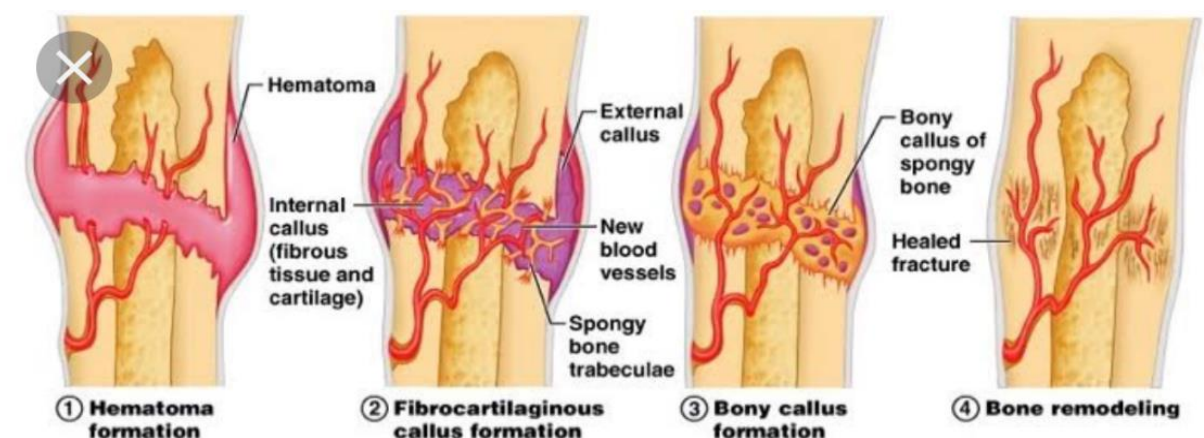
- **External callus** : to the outside under the periosteum .

- **Internal callus** : in medullary canal .

- **Intermediate or permanent callus** : found in between the two ends of fractured bones .

8) The **osteoblasts of the intermediate callus** will form the bony callus by progressive mineralization which increase callus stiffness and strength .

9) The **external and internal calli** will be gradually removed by osteoclasts .



➤ Abnormalities of fracture healing (fracture bone) :

1)Non union : due to presence of pieces of **muscles or soft tissues** that prevent union .

(في بعض الحالات و الشخص بيجبس عظمة مكسوره ممكن يدخل جزء من عضلة في النص بين أجزاء العظمة المكسوره و يمنع التئامها)

2)Delayed union : due to **infection , poor blood supply , protein malnutrition , osteoporosis** (هشاشة العظام) and **incomplete fixation** .

3)Fibrous union : when fixation is not complete the osteoblasts will change to **fibroblasts** (metaplasia of osteoblasts) and union takes place by **fibrous tissue** .

(في بعض الحالات ممكن التئام العظم المكسور ما يحصل بالشكل الطبيعي نتيجة ان خلايا ال osteoblasts اتحولت لخلايا fibroblasts و يبدأ العظم المكسور يلحم مع بعضه ب fibrous tissue مثل بعض)

4) False joint : when fixation is not complete the osteoblasts will change to **synovial cells** that may line atrophic callus and a **false joint** may develop known as **pseudo-arthritis** .

(الحالة دي نفس فكرة الي قبلها الفرق بس ان هنا ال osteoblasts بتتحول ل synovial cells ف بدل ما يتكون عظم جديد عشان يلحم العظم المكسور بيتكون مفصل بداله و الحالة دي اسمها pseudo arthritis)

✚ Repair of nervous system :

➤ The central nervous system :

*The nerve cells are **permanent cells** .

*Injury to the central nervous system is **not followed** by extensive regeneration .

(لو جت الاصابه في الجهاز العصبي المركزي و بالاخص في جسم الخلية العصبية مش بيحصل تجديد للخلية المصابه او الميتة , الي بيقرر يتجدد هو الaxon بتاع الخلية العصبية)

*Its limited by the inhibitory influences of the glial and extracellular environment .

- **Steps of CNS repair :**

1-Necrosis and liquefaction of injured area .

2-Microglia (macrophages of CNS) removes debris .

3-Astrocytes (supporting cells) proliferate and replace the lost area (Gliosis or glial scar) (fibrosis)

➤ **The peripheral nerves :**

*The peripheral nervous system has an **intrinsic ability** for regeneration.

- **Steps of peripheral nerve regeneration :**

1-The axon distal to injury becomes irregular and myelin sheath breaks into droplets up to the level of the first node of Ranvier (**Wallerian degeneration**) .

2-Macrophage and Schwann cells remove debris .

3-The Schwann cells (supporting cells) in both the proximal and distal ends proliferate and unit together forming a tube in which new myelin is formed by oligodendroglia .

4-A new axon grows from the proximal segment (axonal sprouts برعم) and elongates gradually until it reaches the required length , and this process take several months .

