



# ***Pathology***

***Subject :***

***Lec no*** ∅ lecture-6 inflammation

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وَقُلْ رَبِّ زِدْنِي عِلْمًا



# Effects of inflammation :

→ Beneficial  
→ harmful  
→ systemic

## A- Beneficial effects :

These act partly through the flow of **exudates** into the tissue & partly by the phagocytic & microbial effects of migrated WBCs. :

→ Fluids + proteins

تخفيف السموم الخارجة من الكبتريا

(1) Dilution of toxins : exudates dilutes chemical and bacterial toxins & enhance their carriage by lymphatics.

تفاح السموم بحل lymphatics

(2) Protective antibodies : The proteins present in the exudates include antibodies , which have been already present in the plasma as a result of previous infection or immunization. These antibodies attack injurious agents in an attempt to destroy them immunologically.

ال (antibodies) نوع من انواع البروتينات الموجودة في Inflammation يتم انتاجها من طرف جهاز المناعة و memory cell ليسرى التعامل مع الجسم الغريب حال وصوله للمرة الثانية للمسام

هو عامل عن Active form Factor 1

Normal tissue الى Normal tissue (Inflammation) ليميع المواد الصلبة من الدم حول الى

\* يتم انتاج (Fibrin) في منطقة (Fibrin) في منطقة  
منع انتشار البكتيريا

**Fibrin formation :** Fibrinogen of the blood is included in the exudates which is transformed into fibrin . A network of the deposited fibrin is seen in the inflamed tissue forming a mechanical barrier that precludes the movement & spread of bacteria, it may also aid in their phagocytosis.

**(4) Promotion of immunity :**

Bacteria in the inflammatory exudates , whether free or phagocytosed , are carried to the lymph nodes by lymphatics. There they mount an immune response, which provides antibodies & cellular mechanisms that may appear after few days and may remain for years. These immunological mechanisms help destroy microbial agents.

\* تكون (Lymphocytes) = اجل  
Lymph nodes ← antibodies  
cellular mechanisms  
تؤدي الى قتل Microbial agent

\* يكون (swelling) حطيرتها يكون حيز مكان (restricted) من acute laryngitis ← يزداد في الرضعات (suffocation) من الأطفال

# B-Harmful effects :

→ Caused by transudate & exudate

1 Swelling : of acutely inflamed tissue may have serious mechanical effects e.g in acute laryngitis causes suffocation in children

2 Rise in tissue pressure: blood vessels ← ما يزداد في زيادة الضغط ← inter cranial pressure ما يحدث في الدماغ يزداد إلى زيادة الضغط ← ما يحدث في خلايا و cell function & ischemia

Inflammation when is confined within a restricted space cannot expand, the result is an increase in tissue pressure and this interferes with cell function and the blood flow, the latter leads to ischemic injury, e.g. encephalitis and meningitis both cause increased intra cranial pressure and even death.

Similarly osteomyelitis leads to bone necrosis due to ischemia caused by pressure on blood vessels.

3 Sever allergic reaction: e.g. to pollen may cause sever asthma & dyspnoea , this may sometimes be so sever as to cause death due to asphyxia caused by laryngeal edema.

\* قد يكون تعامل الجسم مع اللقاح و ذلك من الاحتجاج (asphyxia)

يتكون العظام من

تحدث في العظام عندما يلتصق spongy bone  
 يزداد في الرضعات و Swelling و ذلك لكن لا يتوسع compact bone  
 يزداد في الرضعات و pressure و ذلك blood vessels  
 فيقتل blood flow و ذلك ischemia

العظم المالحين

Compact bone  
 و هو صلب 1/4

العظم الناعم spongy bone  
 و هو عظم أقل كثافة

# SYSTEMIC EFFECTS OF INFLAMMATION

These effects are collectively called acute-phase reaction.

They include <sup>①</sup> fever, <sup>②</sup> malaise (feeling of being sick), <sup>③</sup> anorexia (loss of appetite), <sup>④</sup> insomnia, <sup>⑤</sup> hypotension, <sup>⑥</sup> accelerated degradation of skeletal muscle <sup>⑦</sup> proteins, increased hepatic synthesis of a variety of proteins (e.g., complement & coagulation proteins), & alteration in the circulating WBC as leukocytosis.

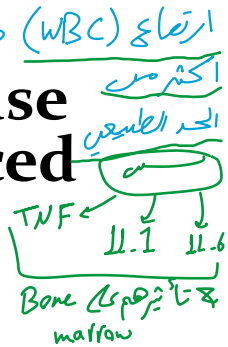
The most important mediators of the acute-phase reaction are the cytokines TNF, IL-1, & IL-6, produced mainly by WBC in response to infection, or to immune & toxic injury, & are released systemically, frequently in a cascade.

TNF & IL-1 both act on the thermoregulatory center of the hypothalamus-via local PGE production to induce fever.

\* العوامل من (1-5) تحدث بسبب IL-1 TNF

\* Synthesis of hepatic proteins occurs under the control of (IL-6) <sup>عصب وظيفته الالتهابي</sup>

منه من plasma derived mediator



active myocine

مقدار الشهية

تعرف وارجاع

اجاب

تغير



IL-6 stimulates the hepatic synthesis of several plasma proteins,

(1) **Fibrinogen; elevated fibrinogen levels** cause RBC to agglutinate more readily, explaining why inflammation is associated with a **higher ESR**.

(2) **C-reactive protein (CRP) & serum amyloid A (SAA) proteins**, both bind to microbial cell walls, & they may act as **opsonins** & fix complement, thus promoting the elimination of the microbes.

\* يوزن من جسم الانسان (5) انواع من (WBC) لا يرتفع معدل جميعها في Inflammation بل انواع معينة من الحالة الحادة

Leukocytosis (increased, mature, white blood cell count in blood) is a common feature of inflammatory reactions, especially those induced by bacterial infection.

- ① neutrophils
- ② eosinophiles  
↳ in parasitic infection
- ③ Lymphocytes
- ④ Monocytes
- ⑤ basophiles

WBC count typically increases from a **normal 4,000 to 10,000 to 15,000 - 20,000 cells per micro liter**, but may climb as high as 40,000 to 100,000, a so-called **Leukemoid (leukemia-like) reaction**.

WBC

- Leukocytosis → 15,000 - 20,000 → inflammation
- Leukemoid (Leukemia like reaction) → 40,000 - 100,000 → leukemia

عدد ما 4000-10,000 من النوع الطبيعي

Most bacterial infections induce selective increase in polymorphonuclear cells called (neutrophilia),

in acute inflammation

□ while parasitic infections & allergic responses characteristically induce eosinophilia.

□ Certain viruses like infectious mononucleosis, mumps, & rubella cause selective ↑ in lymphocytes (lymphocytosis).

①

②

③

□ However, most viral infections, rickettsial, protozoal, & certain types of bacterial infections (e.g., typhoid fever), are associated with a decreased number of circulating WBC called (leucopenia)

Severe bacterial infections (sepsis), especially by gram-negative bacteria stimulate the production of huge quantities of several cytokines, notably TNF, IL-1, IL-6, & IL-8, resulting in septic shock, which is usually fatal.





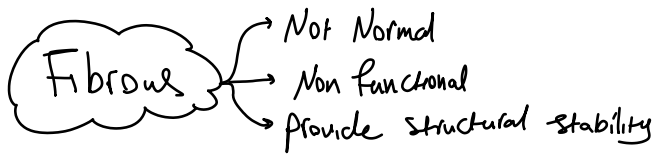
# Healing & Repair

## Introduction :

When injury & any associated acute inflammatory response has resulted in necrosis of specialized cells and damage to the surrounding matrix, the host response must include attempts at replacement of the dead cells by healthy tissues.

This response is referred to as healing, and comprises two processes:

- ① **Regeneration** : replacement of the specialized cells by proliferation of those surviving.   
استبدال الخلايا بخلايا من نفس النوع (نفس الشكل الوظيفي)
- ② **Connective tissue response** : called **repair**, characterized by the formation of granulation tissue and its subsequent maturation i.e. fibrous scar formation.  
\* تنقسم الخلايا من المنطقة التي تم تدميرها لتشكيل خلايا الخلايا المتكسرة



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

Commonly, repair involves a combination of both **regeneration & scar formation in varying degrees** .  
→ like liver cirrhosis

**Fibrosis:** describe the **extensive deposition of collagen** that occurs in the organs as a consequence of **chronic inflammation**, or **infarction**, e.g., myocardium, lungs, liver, kidney, & other organs.

If fibrosis develops in a tissue space occupied by an inflammatory exudate it is called **organization** (e.g., **organizing pneumonia**, **organizing pleurisy**).

Typy 1 ←

این میخورد

To understand repair, we have to know the

- (1) Control of **cell proliferation** . → انقسام الخلايا
- (2) The roles of **stem cells (SC)** in tissue homeostasis.
- (3) Functions of the **Extra Cellular Matrix (EXM)** & how it is involved in repair.  
The roles of **Growth Factors (GF)** in the proliferation of different cell types involved in repair.

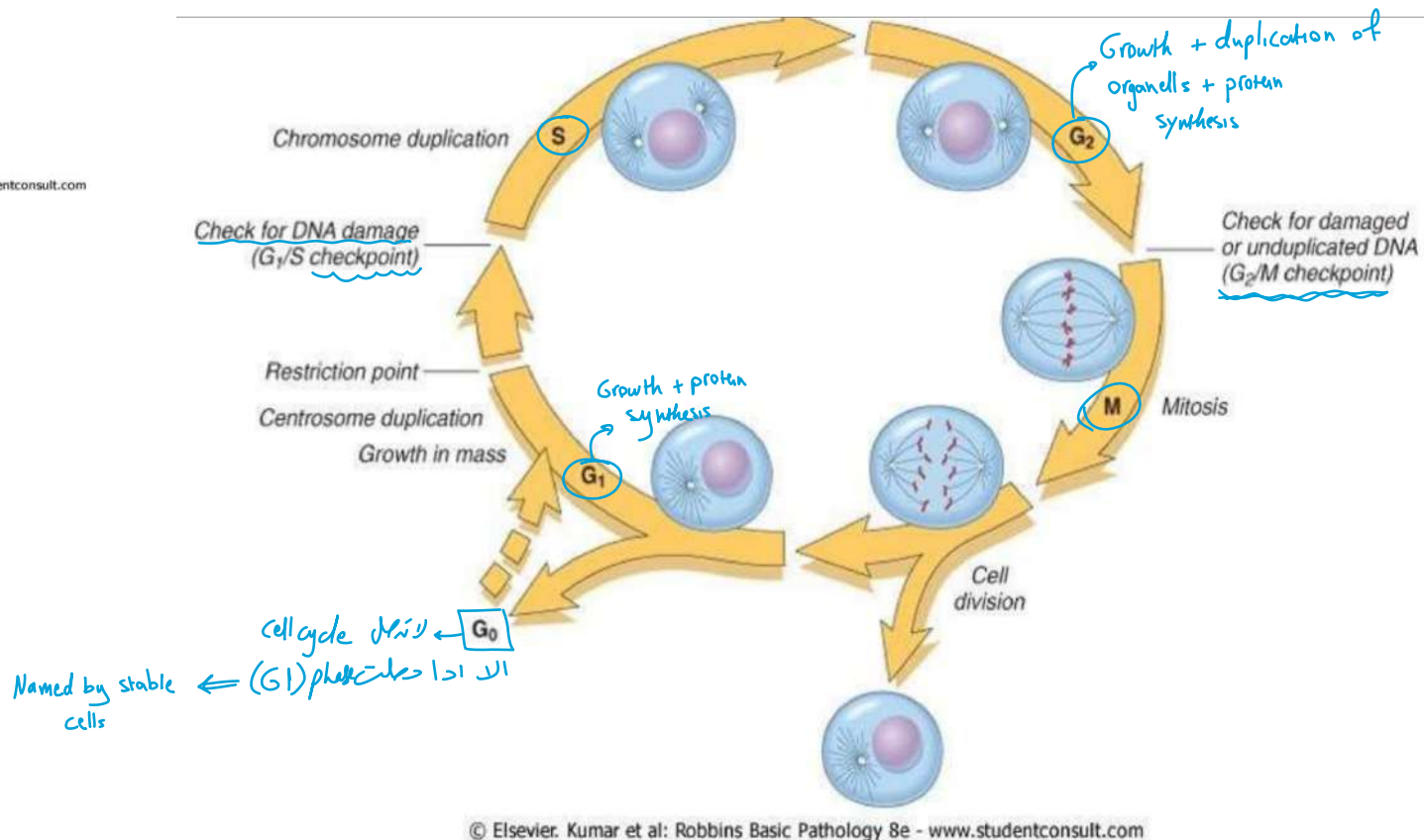
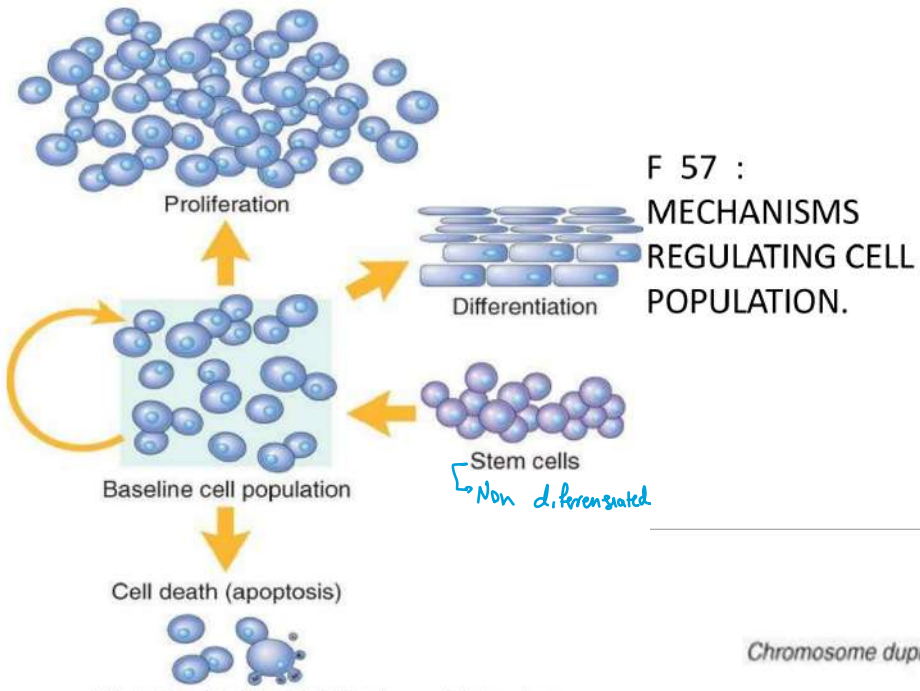
## I- The Cell Cycle

The key process in the proliferation of cells, are DNA replication & mitosis. The sequence of events that control these 2 processes is known as the cell cycle.

**The cell cycle consists of the:**

- (1) Presynthetic growth phase 1 (G<sub>1</sub>)**
- (2) DNA - synthetic phase , or (S)**
- (3) Premitotic growth phase 2 (G<sub>2</sub>)**
- (4) Mitotic phase (M).**





**Figure 58 : Cell cycle . Diagrammatic view .**

F3-3: Cell cycle stages

Somatic cells are divided into : (Functional + well differentiated)

\* هذه التسمية تأتي مع قدر الخلايا مع الانقسام

1) **Labile cells** : These cells are **capable of regeneration** , they have **short life span** and can **multiply throughout life under normal conditions**, like **skin epidermal cells** , **gastro intestinal tract, respiratory tract** , **genitor urinary tract lining epithelial cells & bone marrow cells** , after injury these cells undergo **regeneration with complete restoration of the normal architecture particularly** if the injury is mild and transient.

2) **Stable cells** : These cells undergo multiplication during **embryogenesis** , but then cease multiplication when growth ceases. They have longer life span and slower mitotic rate.

\* في الوضع الطبيعي يكونوا في (G0) لكن قد يدخلوا (G1) مع دورة الخلية في ظروف معينة embryogenesis multiplicity

They retain their mitotic activity during adult life and can undergo **proliferation** when **stimulated after injury**, so that some regeneration of dead tissue occurs in such cells like **liver cells** , **renal** , **adrenal** , **pancreatic cells** also the **fibroblasts and osteoblasts**.

3) **Permanent cells** : Such cells are highly specialized like **neurons** , **the myocardial** & **the striated muscle cells** . They have very long life span and no mitotic activity, once injured they never regenerate → in the case of injury it will be replaced by scar tissue

لن تقسم أبداً

## II- Role of Stem cells :

### Stem Cells (SC)

differentiated Functional } cell cycle  $\text{CPT} > 1 > 1$  } No function undifferentiated (الخلايا الجذعية) لا تفرغ \* MP \*

In most continuously dividing tissues, the mature cells are terminally differentiated & short-lived .

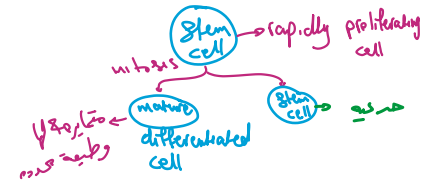
As mature cells die in these tissues, they are replaced by the differentiation of cells generated from their Stem Cells .

Therefore, there is a **homeostatic equilibrium** between the: من هنا 2 الخلايا  
والبقا

- (a) Replication & differentiation of SC, &
- (b) The death of the mature fully differentiated cells.

Skin epidermis & the GIT epithelium, are good examples . In both, SC have been identified near the basal layer of the epithelium.

Stem Cells are characterized by two important properties:



A. . **Self-renewal capacity** → قدرتها على تجديد نفسها

B. . **Asymmetric replication**, → بوسيط من الخلايا غير المتماثلين

which means, that after each cell division some progeny enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity.

بعض الخلايا يدخلون في مسار differentiation (مستقر) ←

SC with the capacity to generate multiple cell lineages → أكثر من نوع من الخلايا

**(pluripotent Stem Cells)** → \* مثال على stem cells تعطي أكثر من نوع من mature cells

Stem cells are of two kinds :

تعطي جميع خلايا الجسم لا استثناء ←

1- Embryonic stem cells ( ES cells ) : These are **the most undifferentiated stem cells** , they are **present in the inner cell mass of the blastocyst** , and **have extensive cell renewal capacity** . Under appropriate culture conditions ES cell can be induced to **form cells of all three germ layers** ,like neurons, cardiac myocytes , liver cells ...etc .

- ① Mesoderm
  - ② Ectoderm
  - ③ Endoderm
- } تنقسم خلايا الجسم



2- **Adult stem cells** : also called **tissue stem cells** , these are less undifferentiated than **ES cells** and are found among **differentiated tissues & organs** .

Although like ES cells have **self-renewal capacity** , but it is a **limited property** , and their **lineage potential** i.e. ability to give rise to specialized cells restricted to some or all the differentiated cells of that tissue or organ . These are present in the **bone marrow** & several other tissues of the adult individuals.

The most extensively studied **tissue or adult stem cells** are the **hematopoietic stem cells** found in the bone marrow , as well as from peripheral blood , after mobilization by certain cytokines like **granulocyte colony- stimulating factor (G-CSF)**

عوامل تحريك من نخاع العظام

جميع الخلايا (WBC) RBC platelets

poly potent

تكاثر الخلايا (stem cell) bone marrow

اصعب من الembryonic

قدرة على انقسام الخلايا mature

اقل من embryonic

تكاثر (stem cell) تنظيم الخلايا (تكاثر) وجودها في اية عضو حيث انها تنظم نوع الخلايا التي لها نسبة ويرجعها (stem cell) تكاثر الخلايا (stem cell)

**Bone marrow SC** have very broad differentiation capabilities . They can differentiate into all blood cells lineage as well as being able to generate fat, muscle, cartilage, bone, & endothelium (EC).

multiple cell lineages ←

In clinical practice , marrow stem cells are used for treatment of leukemia & lymphoma .

The ability to identify & isolate stem cells have given rise to the new field of ( Regenerative Medicine ) its main goal, is the regeneration & repopulation of damaged organs (e.g., Myocardial Infarction ) using Embryonal Stem cells or adult SC.

to generate new cells

One of the most exciting prospects in this field is of SC therapy known as (therapeutic cloning) .

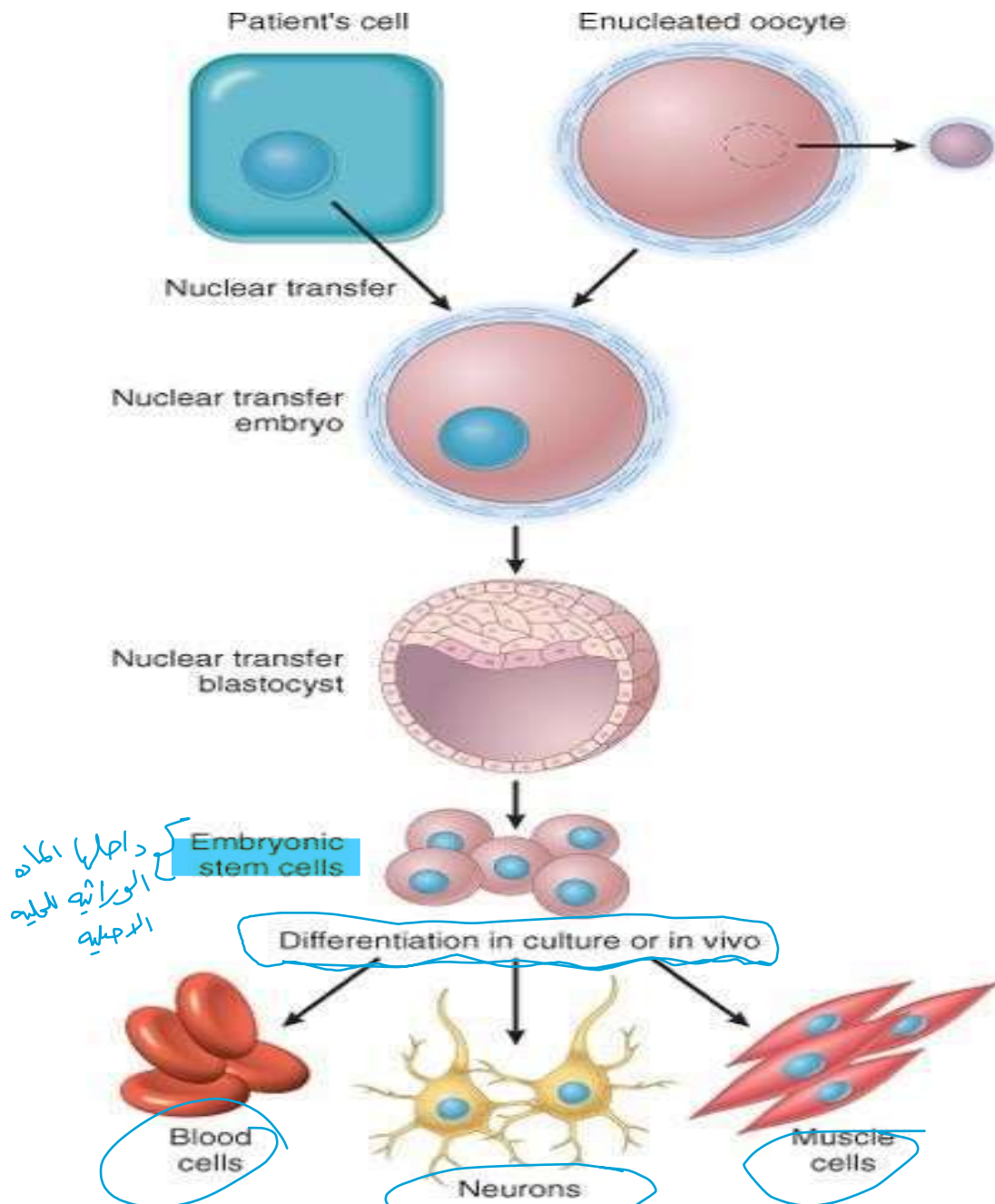
توليد الخلايا الجذعية

# The main steps involved in therapeutic cloning, using ES cells for cell therapy .

In this procedure:

- (1) The **diploid nucleus** of a cell <sup>(2n)</sup> (e.g., WBC) from a patient (e.g., with MI or CVA) is introduced into an **enucleated oocyte**. → ذریعہ دون نواہ
- (2) The oocyte is activated & the zygote divides to become a **blastocyst** containing donor DNA.
- (3) The blastocyst is dissociated to obtain **ES cells** ;
- (4) ES cells are capable of differentiating into various tissues (e.g., myocytes or neurons), either in culture or after transplantation into the donor.

**The goal** is to repopulate the damaged heart or brain cells of the patient, using the patient's cells himself, thus avoiding immunologic rejection.



**F 59 : Steps involved in therapeutic cloning, using embryonic stem (ES) cells for cell therapy.**



### III- Extra cellular Matrix (ECM) & Cell-Matrix Interactions

ECM is a dynamic, constantly remolding macromolecular complex, synthesized locally, arranged into a network that surrounds cells, & constituting a significant proportion of any tissue. ECM sequesters water, providing firmness to soft tissue & minerals, giving rigidity to bone.

*Handwritten notes:*  
- Proteins, Lipids, Carbohydrates (pointing to macromolecular complex)  
- WBC (pointing to network)  
- by Fibroblast (pointing to synthesized locally)  
- 3 (circled, pointing to firmness)  
- 5 (circled, pointing to rigidity)

By supplying cell adhesion & a reservoir for Growth Factors (GF), ECM regulate the movement, proliferation, & differentiation of the cells within it

*Handwritten notes:*  
- 6 (circled, pointing to cell adhesion)  
- 7 (circled, pointing to reservoir)  
- 8 (circled, pointing to regulate)  
- 9 (circled, pointing to proliferation)

ECM occurs in 2 basic forms:

- ① Interstitial matrix
  - ② Basement Membrane.
- } types of ECM

## Interstitial Matrix :

Present in: (1) the spaces **between cells in connective tissue** .

(2) **between epithelium & the supportive vascular & smooth muscle structures.**

Inter-  
stitial Matrix  
Its major constituents are:

① fibrillar collagen (types I, II, III, V)

② nonfibrillar (IV) collagens

③ fibronectin → adhesion molecule

④ elastin

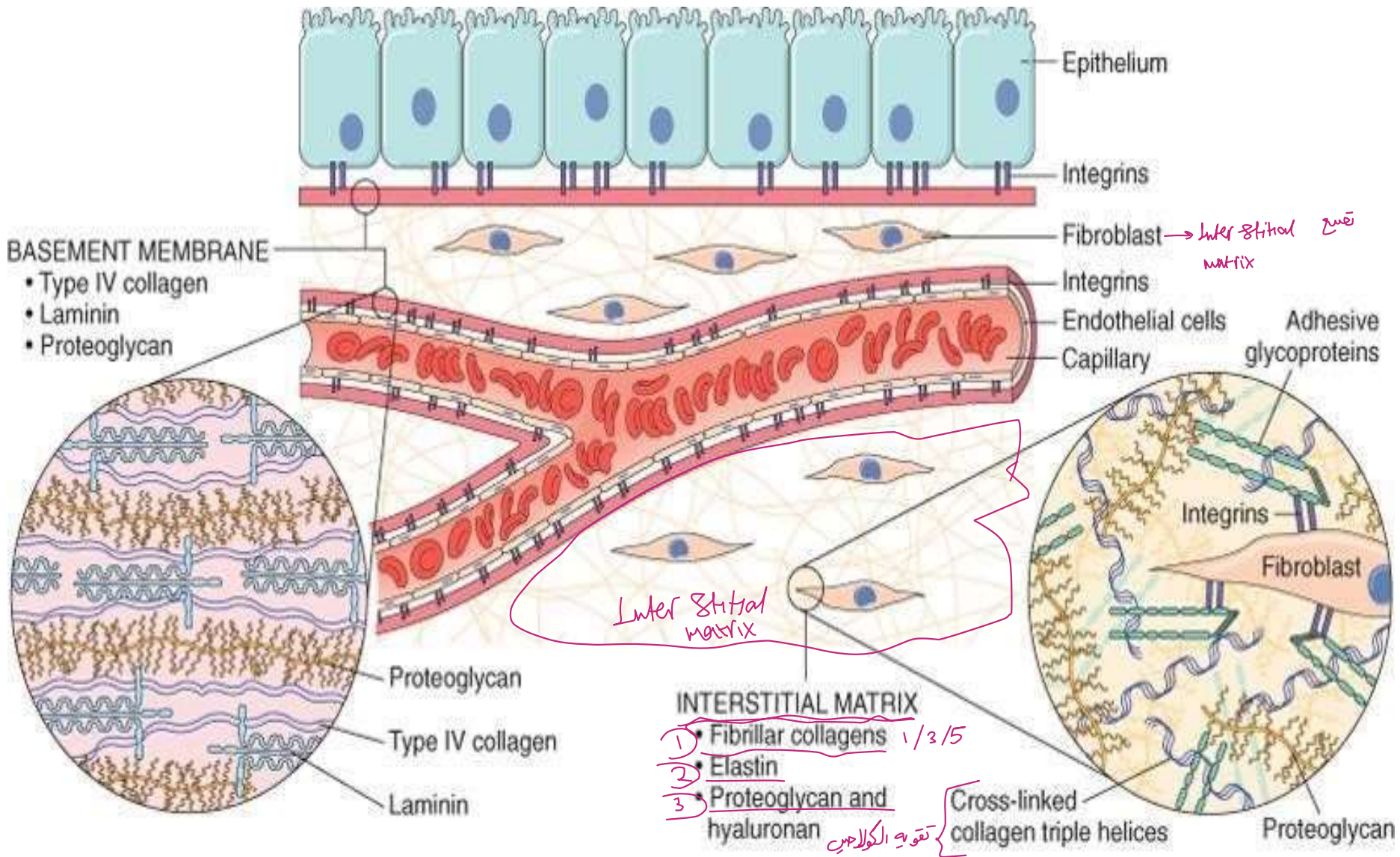
⑤ proteoglycan } Glucose amino glycans  
(GAGs) يتكونوا من سلاسل

⑥ hyaluronate & others.

It is synthesized by mesenchymal cells (e.g. fibroblasts) & tends to form a **three-dimensional amorphous gel**.

Inter-  
stitial  
Matrix

# F 60 : Major components of Extra Cellular Matrix (ECM)



**Basement membrane (BM) :** → يوجد تحت طبقة epithelium

The interstitial matrix in connective tissues becomes highly organized around epithelial cells Epithelial Cells & Smooth Muscle Cells forming the specialized BM.

BM lies (sits) beneath epithelium forming a plate - like chicken wire mesh.

BM major constituents are laminin + amorphous non fibrillar type IV collagen , and proteoglycan .

① cell adhesion  
② mesenchymal cell  
③ epithelium

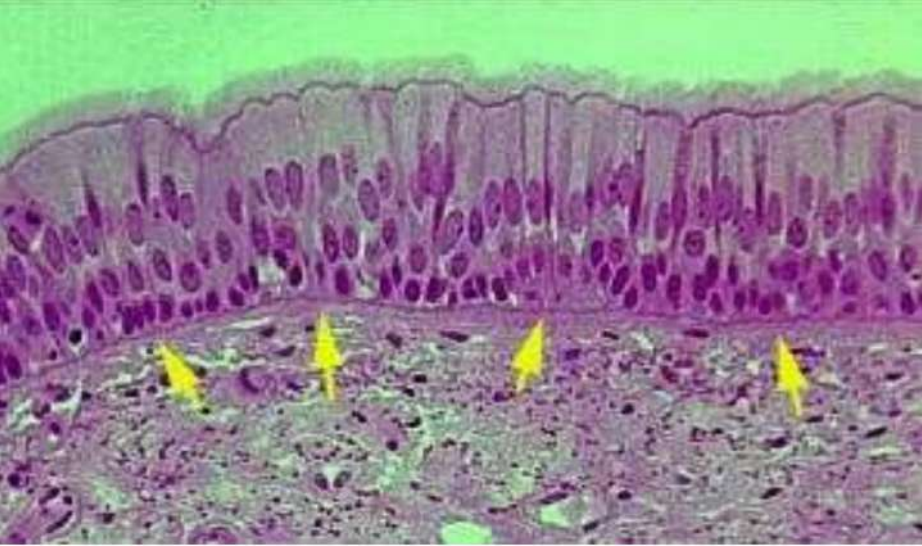
الطبقة تحتها  
التي فوقه

Basement membrane

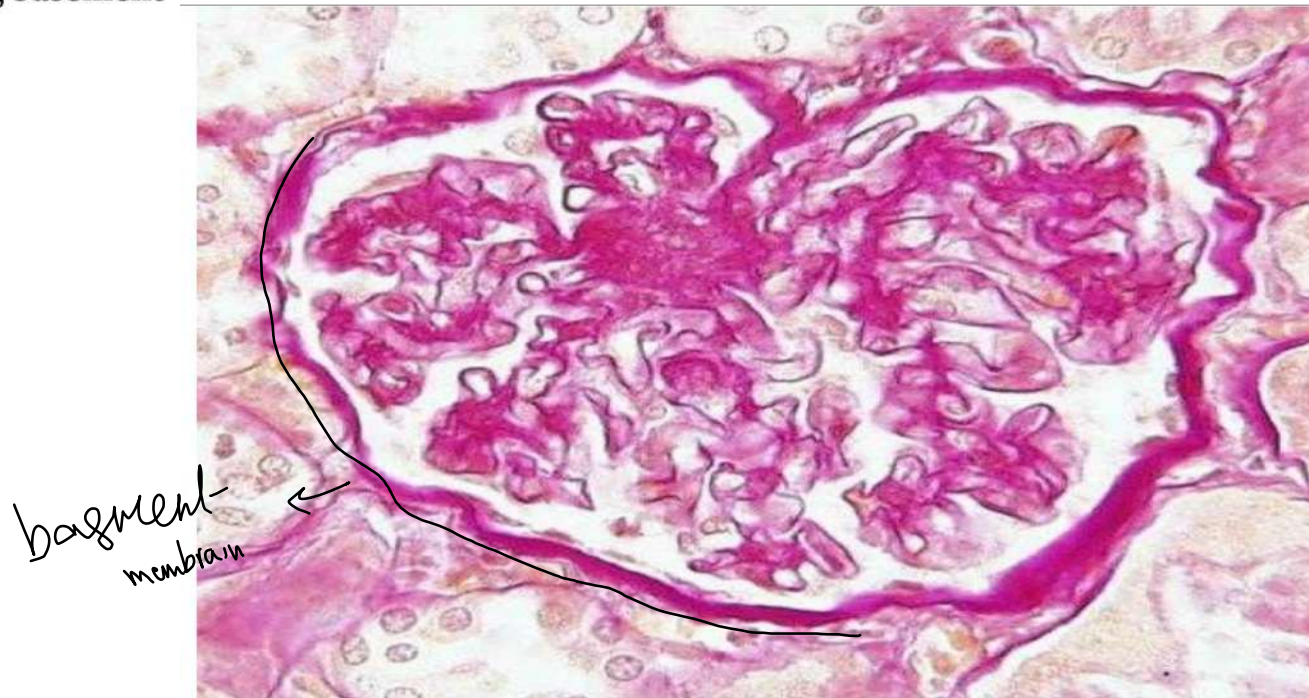
It is formed by the underlying mesenchymal cells & overlying epithelium.

\*all of the following are component of interstitial matrix except? laminin





**Figure 61 : Bronchial mucosa showing basement membrane (arrows)**



**Figure 62 : Renal glomerulus showing basement membrane (pink colored)**