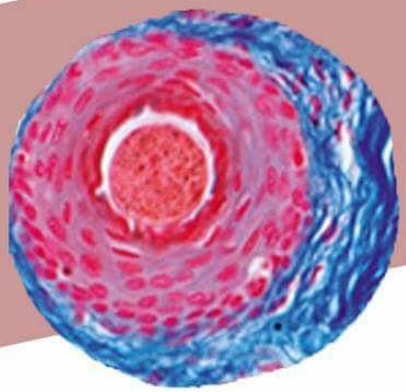
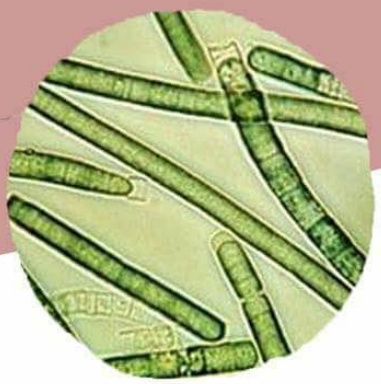
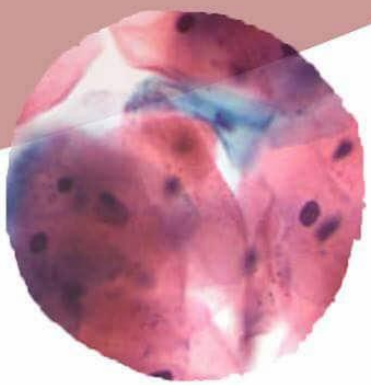
INTRODUCTION TO PATHOLOGY

Done by Ola Al-juneidi

Corrected by Manar Alafeshat

Sheet# 13

Recall:

Last time we talked about growth factors (GFs) and how they are responsible for the entry of cells into the cell cycle and protein synthesis. Actually, GFs are responsible for all the processes of growth and even the inhibition of growth of cells.

Most GFs are proteins, but some of them are steroids. Receptors are either inside the cell or outside the cell. Ligands for the receptors, which are inside the cells are hydrophobic (e.g. Vitamin D, steroid and thyroid hormones).

Signaling of Growth Factors

How do GFs act?They act as ligands.

Cells have receptors on their membranes; most of these receptors are transmembrane receptors. The purpose of the binding of any ligand to its receptor is to send a message to the nucleus.

How is this message sent? By certain proteins (messengers). Therefore, binding of a ligand to its receptor stimulates a number of proteins to convey the message to the nucleus. Thus, transcribing certain parts of the DNA or inhibiting transcription of DNA.

How are these protein activated after binding of the ligand? By phosphorylation (adding a phosphate group /PO_4^{-3}) by using ATP, the most important source of energy for our cells.

Recap:

To stimulate growth by a growth factor, it has to bind to a receptor. This binding will stimulate certain proteins by phosphorylation, which is in the majority of cases (but not always) mediated by ATP. This then sends a message to the nucleus ,thus stimulating or inhibiting the transcription of certain DNA sequences.

Growth Factors'Receptors

*All 3 types of receptors need a source of phosphate (usually ATP). So they mostly need kinases.

1- Receptors with intrinsic kinase activity:

-Part of these receptors is the kinase; they are self-sufficient. They can phosphorylate themselves.

-When the ligand binds its receptor, 2 things happen:

1. Dimerization: two receptors couple (making a dimer).
2. Phosphorylation: the binding of the ligand (GF) and the dimerization stimulates the kinase in the receptor, so it phosphorylates the tyrosine residues in the same receptor. Now the receptor is active and can convey the message to the nucleus.

-Used by: EGF (epidermal GF) and HGF (hepatocyte GF).

-The most important 2nd messengers used here are RAS protein (its mutation is one of the most common mutations that can cause cancer) also phosphastidylinositol 3 kinase and phospholipase c sigma which lead to cell proliferation.

00:00-14:45

2- G-protein coupled receptors:

-These receptors don't use ATP and kinases. They actually use GTP instead. These receptors are proteins with 7 transmembrane α-helices.

-They are linked to a G protein. The G protein consists of 3 subunits: α, β, and γ. When the G protein is bound to GDP, it's inactive. Binding of the ligand (usually a chemokine) to its receptor causes the exchange of GDP for GTP; it's

now activated. The signal is now transduced to the nucleus through 2nd messengers (e.g. influx of Ca^{+2}, cAMP and IP3 pathway).

-Here we also need phosphorylation, but the phosphate is not coming from ATP. Instead, we get the phosphate from GTP.

*What is the difference between ATP and GTP?

-ATP gives a phosphate group to any reaction. While GTP is mainly used in protein synthesis; it's more specific than ATP.

3- Receptors without intrinsic enzymatic activity:

-They can't do the phosphorylation by themselves because they don't have an intrinsic kinase activity. However, when the ligand (usually a cytokine) binds this kind of receptor, it uses the kinases present in the cytoplasm.
How? Binding of the ligand causes a conformational change in the receptor so it can bind a kinase from the cytoplasm. This kinase is called JAK (**J**ust **A**nother **K**inase/ **JA**nus **K**inase). They named it Janus kinase because it has two sides; one phosphorylates and the other inhibits phosphorylation (Janus is a Greek god believed to have 2 faces).
Once this happens (activation of the kinase and phosphorylation of certain proteins) the 2nd messenger is transferred to the **nucleus** with the help of proteins called STAT proteins (**S**ignal **T**ransducers and **A**ctivators of **T**ranscription proteins). This pathway is called the JAK-STAT pathway.

14:45-21:20

The Extracellular Matrix

Recall:

*Tissue repair can either happen by regeneration or scarring according to the type of injury and the injured tissue.

*If we can fix it → regeneration
If we can't fix it (severe injury / the tissue can't regenerate) → scarring

*If the extracellular matrix is disturbed → fibrosis and scarring

The extracellular matrix (ECM) is very important. It is the supportive tissue for all the epithelial and endothelial structures that we have. If the integrity of the ECM after an injury is still not disturbed, regeneration will occur. Any injury that affects the integrity of the ECM will end with scarring.

The ECM is composed of:

- **Fibrillary material** (strong fibers).
- **Amorphous material** (gel-like) to give support. At the same time, it should not be that hard.

Some tissues need stronger support than others so they need strong fibers; such as: skin, blood vessels. Other tissues must be flexible such as joints so they need some sort of amorphous material around them to give support and flexibility at the same time.

(Fibrillary part of ECM) There are two kinds of fibers :

***1-Collagen*:**

That gives *strength*. That's why fibrosis that happens during wound healing is mostly collagenous. It has a triple helix structure. The 3 helices are attached to each other by lysine. How? By enzymes that crosslink them together, these are lysyl oxidase & lysyl hydroxylase. These enzymes are very important to give strength to collagen. Lysyl oxidase needs copper and lysyl hydroxylase needs vitamin C.

Collagen is a protein and it is the most important one in wound healing. This means that if a patient has a problem in proteins (e.g. malnutrition, hypoproteinemia, hypoalbuminemia), synthesis of collagen will be defective and this patient will have problems in wound healing. Also, if deficient in vitamin C the patient will have scurvy. One of the symptoms of scurvy is poor wound healing because of poor crosslinking of collagen. This poor linking of collagen makes it weak and not strong enough to give support causing bleeding of the gums along with other symptoms.

The 2 types of collagen are:

1. Fibrillary collagen:Types I, II, III, and V.It's important for giving strength and it needs vitamin C.
2. Non-fibrillary collagen: Types IV (in basement membranes), VII, and IX.
   *Basement membranes need collagen fibers (strength) and some flexibility provided by the non-fibrillary collagen type IV.

→**These two genetic diseases are related to collagen synthesis**

- **Osteogenesis imperfecta:**
  The formation of bone is imperfect because of a problem in collagen synthesis.
- **Ehlers-Danlos syndrome:**
  Not enough collagen causing extra flexibility.

2-Elastin:

A protein that gives *elasticity* and allows tissues to recoil (returning to a baseline structure after stretching).
Where do we need elasticity? Blood vessels, skin, lungs (in areas where we need elasticity in addition to support).

Genetic Diseases Affecting the Synthesis of Elastin:

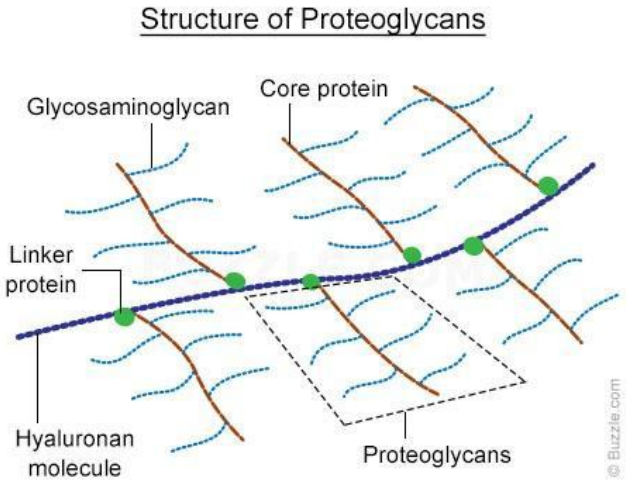
- **Marfan syndrome:**
  It is an inherited congenital defect in the synthesis of elastin fibers (not enough or deformed elastin). People with this disease are abnormally tall with long arms and legs. The most important affected site is the blood vessels (e.g. the aorta); they are weak and suffer from aneurysm.

21:20-32:00

We talked about the fibrillary part of the ECM (which gives support). Now we will continue talking about the non-fibrillary part of the ECM: the amorphous ECM.

Part of the amorphous ECM is the non-fibrillary (amorphous) collagen but it's also composed of:

1. **Proteoglycans:**polysaccharides around a core of protein.
2. **Hyaluronic acid (=hyaluronan):** a sugar without a protein core.



Both give the gel-like nature (e.g. around the joins) to give *lubrication*.

We need a 3rd component to adhere to all the other components, which are:

3. **Adhesive Glycoproteins:**
    a. Laminin:Important for the attachment of the basement membrane to the overlying epithelial cells and the underlying stroma.
    b. Fibronectin
    c. Integrins

Recall: integrins are a type of the adhesion molecules in inflammation.

32:00-37:00

Please refer to the slides for further information that wasn't mentioned in the record.

THE END