

Glycosaminoglycans

complex carbohydrates

Glycosaminoglycans

خوبیله / غیر صغیر / ماکرونت من اکثر من نوعی سکر

➤ Are long, negatively charged, unbranched, heteropolysaccharide chains generally composed of a repeating disaccharide unit [acidic sugar-amino sugar]_n

کدامت = سکریت

شوا انواعی

➤ The amino sugar is either D-glucosamine or D-galactosamine in which the amino group is usually acetylated, thus eliminating its positive charge

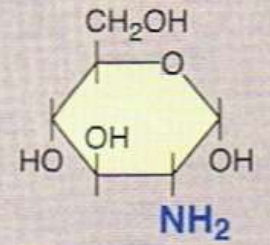
acetyl group ← یکتا محلات الیه acetyl group ← neutral ← یکتا شحنة الموجبة

SO₄⁻ ← یکتا شحنة سالبة قویه

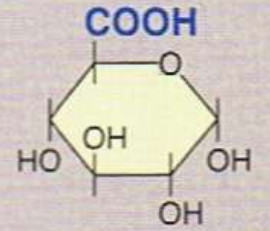
➤ The amino sugar may also be sulfated on carbon 4 or 6 or on a nonacetylated nitrogen.

➤ The acidic sugar is either D-glucuronic acid or its carbon-5 epimer, L-iduronic acid.

epimer → کربونه رقم 5



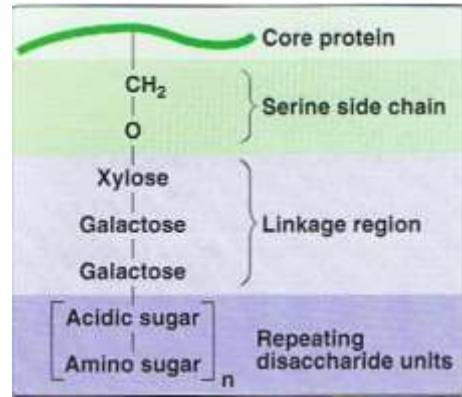
Glucosamine



D-Glucuronic acid



L-Iduronic acid



what are the Functions for Glycosaminoglycans (GAG)?

- These compounds bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body's ground substance.
- The viscous, lubricating properties of mucous secretions are also caused by the presence of glycosaminoglycans, which led to the original naming of these compounds as mucopolysaccharides.
- As essential components of cell surfaces, GAGs play an important role in mediating cell-cell signaling and adhesion.

GAG ماسه قديمه

Classes of GAGs

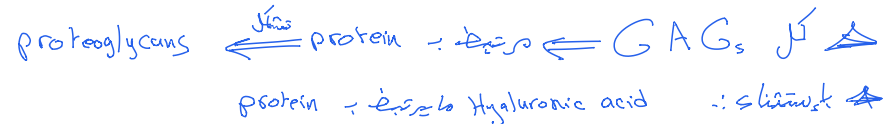
what are

➤ There are six major classes of glycosaminoglycans? including:

- ① ➤ chondroitin 4- and 6-sulfates
- ② ➤ keratan sulfate
- ③ ➤ dermatan sulfate
- ④ ➤ Heparin
- ⑤ ➤ heparan sulfate
- ⑥ ➤ hyaluronic acid.

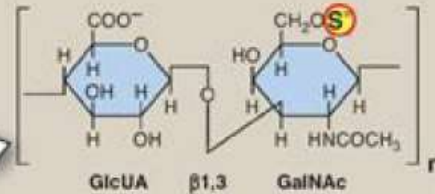
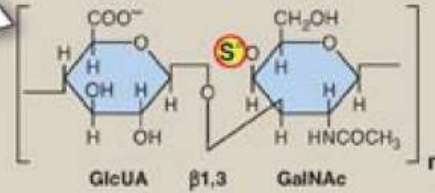
➤ All of the GAGs, except hyaluronic acid, are found covalently attached to protein, forming proteoglycan monomers, which consist of a core protein to which the linear GAG chains are covalently attached

➤ The proteoglycan monomers associate with a molecule of hyaluronic acid to form proteoglycan aggregates.



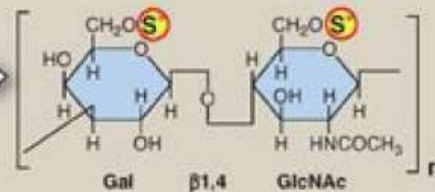
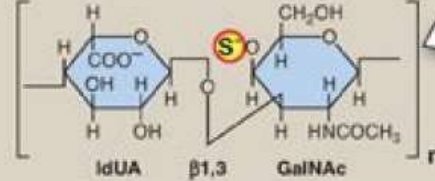
CHONDROITIN 4- AND 6-SULFATES

- Disaccharide unit: N-acetylgalactosamine with sulfate on either C 4 or C 6 and glucuronic acid
- Most abundant GAGs in the body
- Found in cartilage, tendons, ligaments, and aorta
- Form proteoglycan aggregates, often aggregating noncovalently with hyaluronic acid
- In cartilage, bind collagen and hold fibers in a tight, strong network



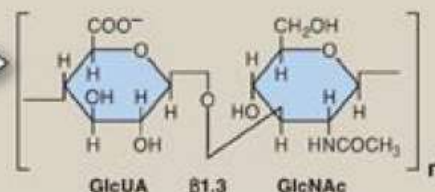
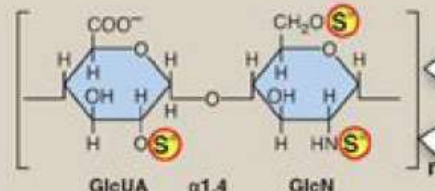
KERATAN SULFATES (KS) I and II

- Disaccharide unit: N-acetylglucosamine and galactose (no uronic acid); variable sulfate content may be present on C 6 of either sugar
- Most heterogeneous GAGs because they contain additional monosaccharides such as L-fucose, N-acetylneuraminic acid, and mannose
- KS I found in corneas; KS II found in loose connective tissue proteoglycan aggregates with chondroitin sulfate



HYALURONIC ACID (HYALURONATE)

- Disaccharide unit: N-acetylglucosamine and glucuronic acid
- Different from other GAGs: unsulfated, not covalently attached to protein, and only GAG not limited to animal tissue, but also found in bacteria
- Serves as a lubricant and shock absorber
- Found in synovial fluid of joints, vitreous humor of the eye, the umbilical cord, loose connective tissue, and cartilage



DERMATAN SULFATE

- Disaccharide unit: N-acetylgalactosamine and L-iduronic acid (with variable amounts of glucuronic acid)
- Found in skin, blood vessels, and heart valves

HEPARIN

- Disaccharide unit: Glucosamine and glucuronic or iduronic acid; most glucosamine residues are bound in sulfamide linkages; sulfate also found on C 3 or C 6 of glucosamine and C 2 of uronic acid (an average of 2.5 S per disaccharide unit)
- α -Linkage joins the sugars
- Unlike other GAGs that are extracellular compounds, heparin is an intracellular component of mast cells that line arteries, especially in liver, lungs, and skin
- Serves as an anticoagulant

HEPARAN SULFATE

- Disaccharide unit: Same as heparin except some glucosamines are acetylated, and there are fewer sulfate groups
- Extracellular GAG found in basement membrane and as a ubiquitous component of cell surfaces

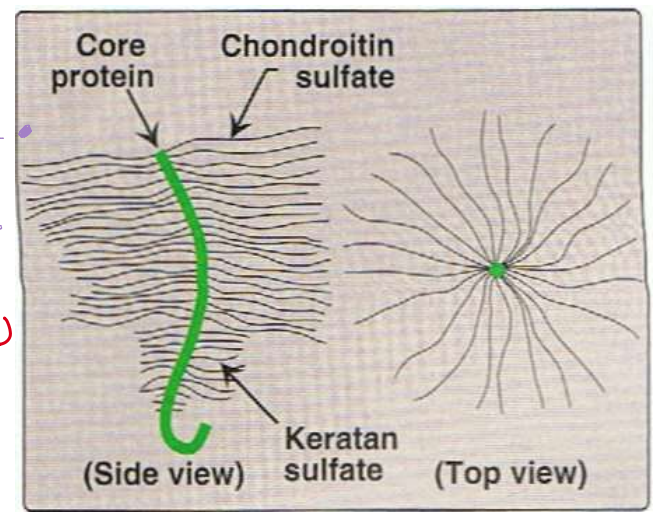
Proteoglycan Structure

- core protein
- GAG chain attached with it

• يتم تجميع مع Hyaluronic acid

• تشكل هياكل هائلة Huge aggregates

(الصورة توضح شكل الفريشة)

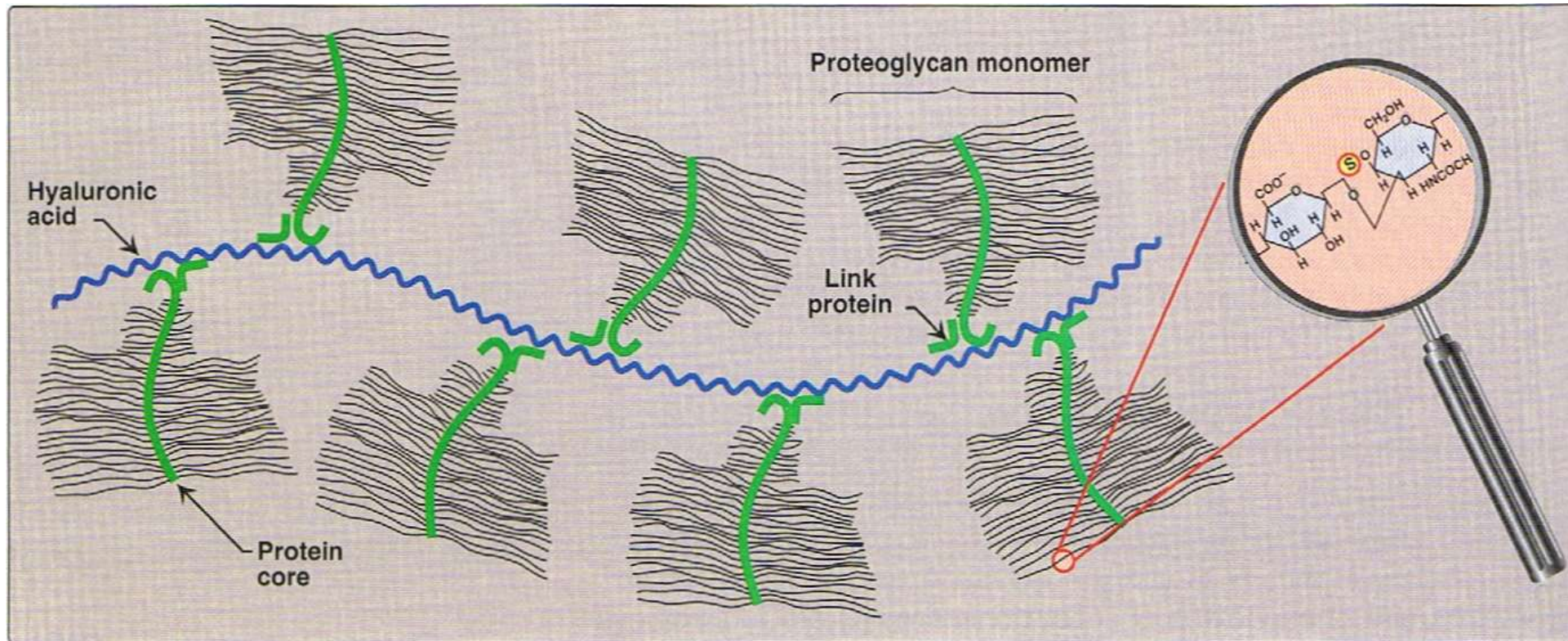


• تضييق :: عمود رئيسي = Hyaluronic acid

• زي الفريشة (brushes) = proteoglycans

هذا يعطي :: قوة + مرونة + إضافة بالكاس (فريشة الأسنان)

• موجودة في ::
• cartilage
• connective tissue



Synthesis of Glycosaminoglycans

where

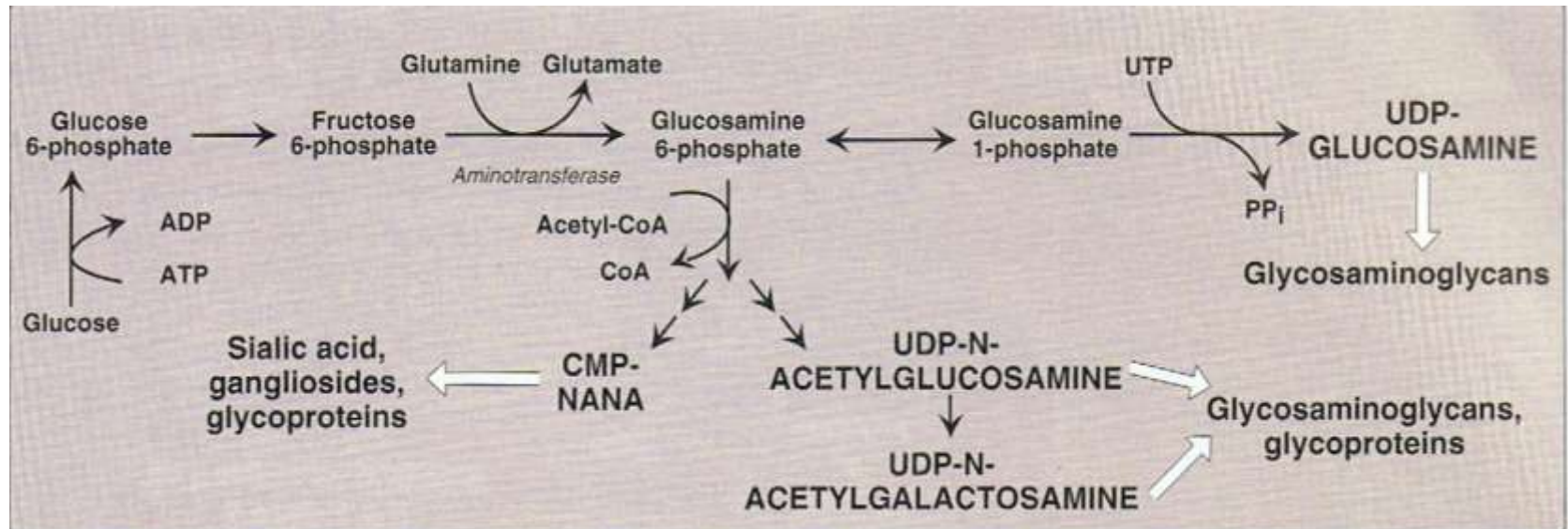
- GAGs are synthesized in the **endoplasmic reticulum** and the **Golgi**

Mechanism of synthesis

- The polysaccharide chains are elongated by the sequential addition of alternating acidic and amino sugars, donated by their UDP-derivatives

what is

- The last step in synthesis is sulfation of some of the amino sugars. The source of the sulfate is 3'-phosphoadenosyl-5'-phosphosulfate.



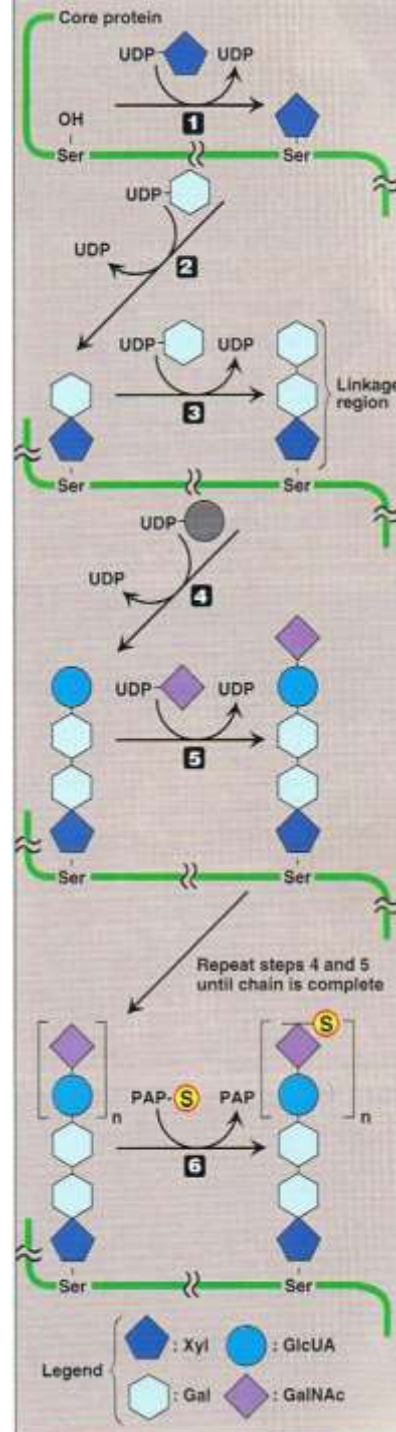
Slide 8: Mechanism (الآلية بالصورة)

الصورة تشرح:

1. يبدأ من **core protein**
2. يضاف:

- Xylose → Galactose → Galactose (linker region)

3. تبدأ إضافة **GAG chain**
4. elongation
5. sulfation



المشكلة

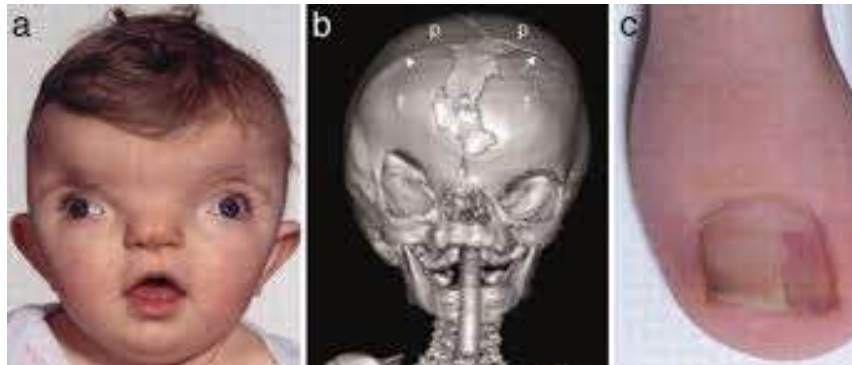
هذا نقص enzyme ← ما نتفكر

تظم (lysosome) في الـ GAGs

Mucopolysaccharidosis

Mucopolysaccharidoses (MPS) are a group of rare, inherited metabolic disorders caused by a deficiency of enzymes needed to break down sugar chains (glycosaminoglycans). This leads to toxic accumulation in cells

- Glycosaminoglycans are degraded by lysosomal hydrolases. They are first broken down to oligosaccharides, which are degraded sequentially from the non-reducing end of each chain
- A deficiency of one of the hydrolases results in a mucopolysaccharidosis.
- These are hereditary disorders in which glycosaminoglycans accumulate in tissues, causing symptoms such as skeletal and extracellular matrix deformities, and mental retardation
- Examples of these genetic diseases include Hunter and Hurler syndromes



Glycoproteins

- Glycoproteins are proteins to which oligosaccharides are covalently attached.
- They differ from the proteoglycans in that the length of the glycoprotein's carbohydrate chain is relatively short (usually two to ten sugar residues long, although they can be longer)
- The carbohydrates of glycoproteins do not have serial repeats as do glycosaminoglycans.

الفرق عن GAGs:

Glycoproteins	GAGs
short chains	long chains
NO repeats	repeating units
functional	mostly structural

What are

Function of glycoproteins?

- Membrane-bound glycoproteins participate in a broad range of cellular phenomena, including:
 - Cell surface recognition (by other cells, hormones, viruses)
 - Cell surface antigenicity (such as the blood group antigens)
 - As components of the extracellular matrix and of the mucins of the gastrointestinal and urogenital tracts, where they act as protective biologic lubricants.
 - Almost all of the globular proteins present in human plasma are glycoproteins.

Synthesis of Glycoproteins

- Glycoproteins are synthesized in the **endoplasmic reticulum** and the **Golgi**.
- The precursors of the carbohydrate components of glycoproteins are **sugar nucleotides**.
- **O-linked glycoproteins** are synthesized by the sequential transfer of **sugars** from their nucleotide carriers to the protein.
تضاف مباشرة الي البروتين Sugars
- **N-linked glycoproteins** contain **varying amounts of mannose**. They are synthesized by the transfer of a pre-formed oligosaccharide from its membrane lipid carrier, **dolichol**, to the protein.
تعمل كحامل واسطة من Dolichol الي Asparagine(Asn)
- They also require **dolichol**, an intermediate carrier of the growing oligosaccharide chain.

Slide 13-14: N-linked pathway

الخطوات:

1. تصنيع البروتين في ER
2. dolichol على oligosaccharide
3. Asn إلى transfer
4. trimming
5. Golgi في modification

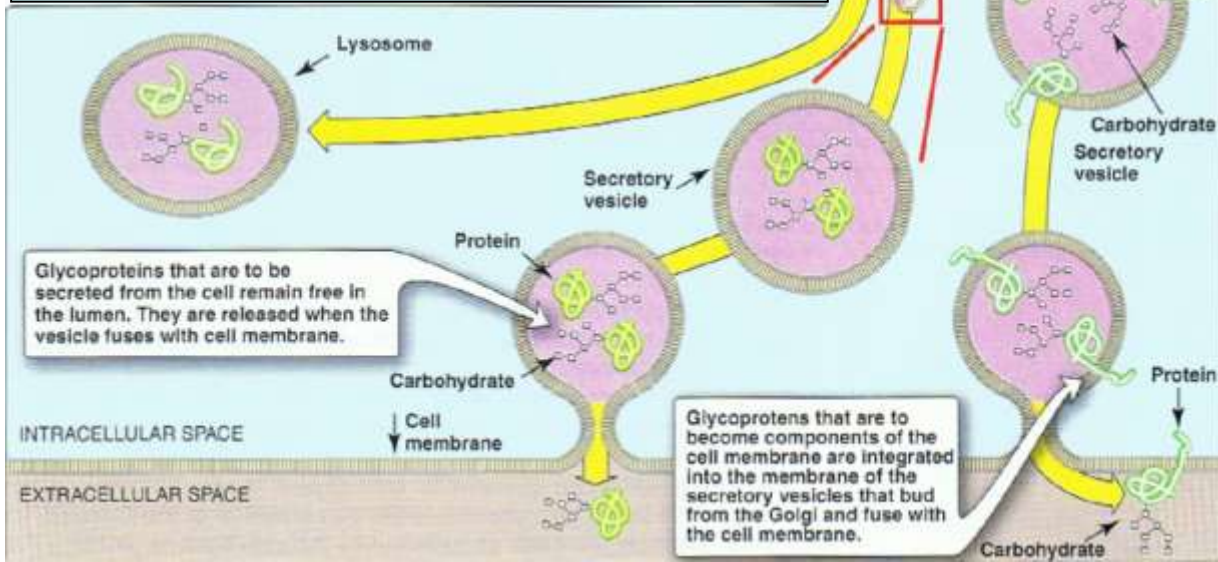
🔥 هذا pathway لازم تفهمه مش تحفظه

ROUGH PLASMATIC RETICULUM (RER)

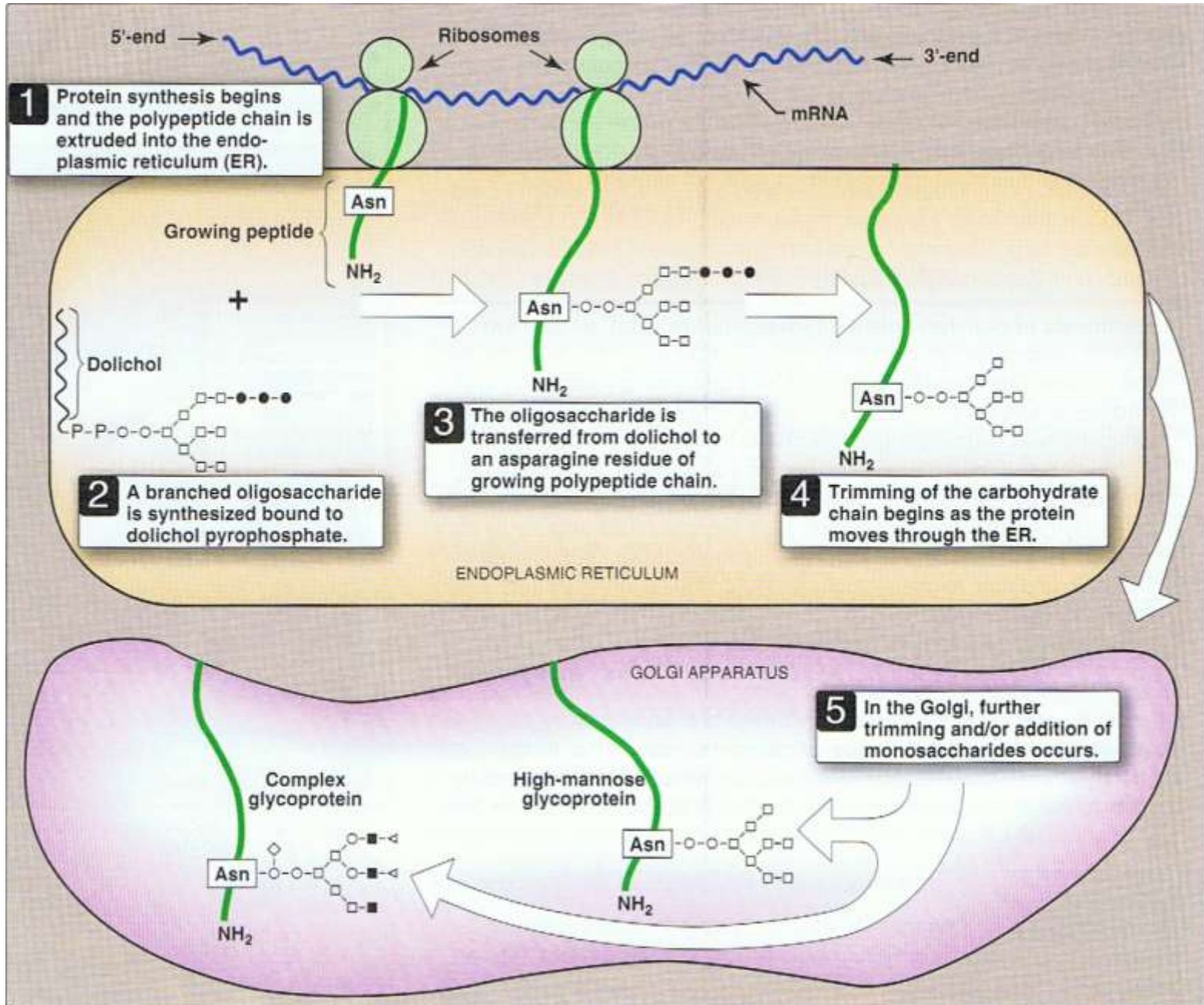
- RER is series of interconnected membrane-bound sacs.
- Ribosomes are bound to the cytosolic side of the membrane.



Vesicles bud off from the Golgi and their contents are targeted to the cell membrane, the extracellular environment, or the lysosomes.



Synthesis of N-linked glycoproteins.



Lysosomal degradation of glycoproteins

- A deficiency in the phosphorylation of mannose residues in N-linked glycoprotein pre-enzymes destined for the lysosomes results in **I-cell disease**
- Glycoproteins are degraded in lysosomes by acid hydrolases
- A deficiency of one of these enzymes results in a glycoprotein storage disease (**oligosaccharidosis**), resulting in accumulation of partially degraded structures in the lysosome

I-cell disease :-

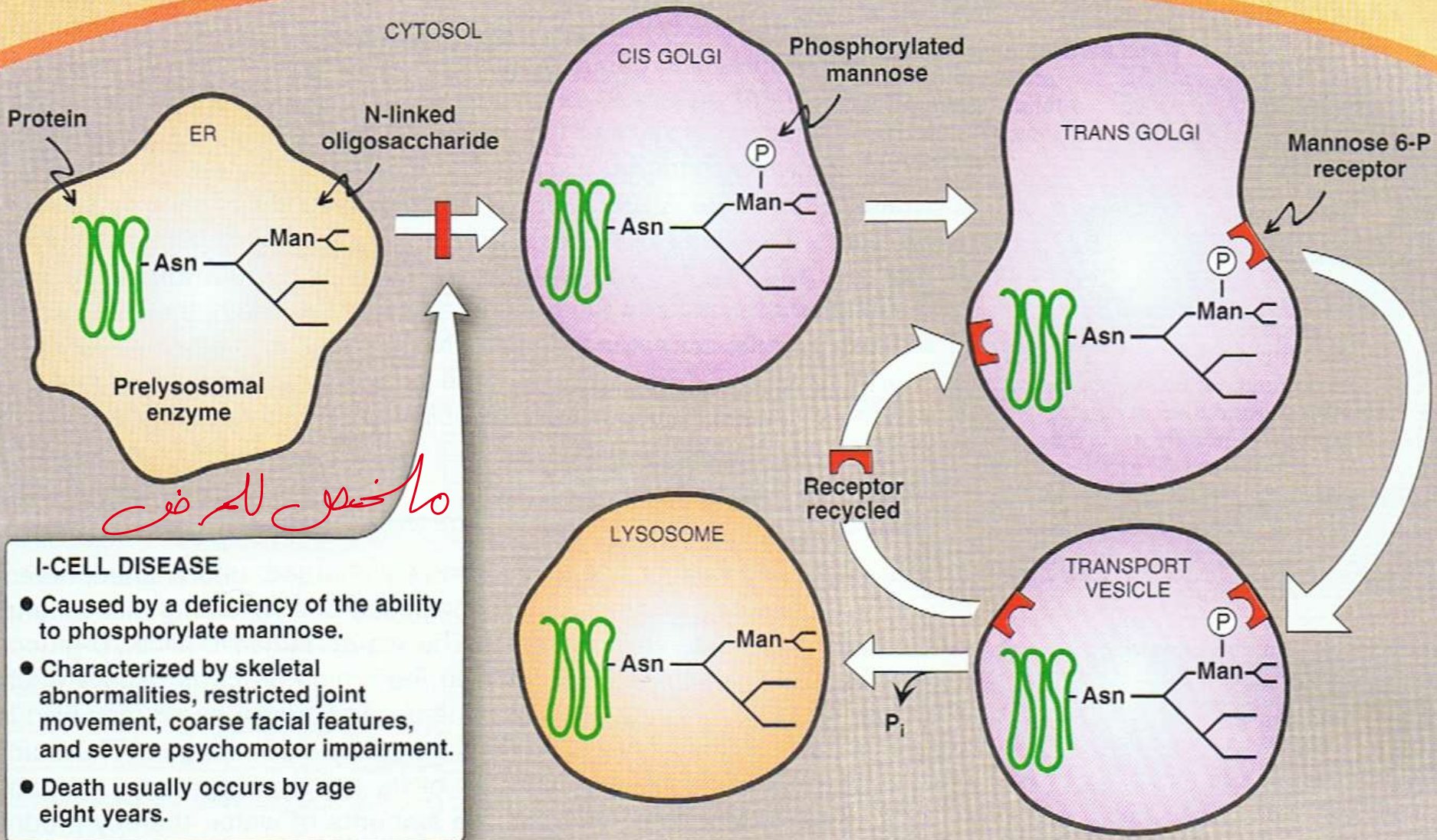
1- Glycoprotein degradation in lysosome
2- If mannose phosphorylation doesn't happen, the enzymes will not go to lysosome

🔥 I-cell disease

المرض:

الأعراض:

- skeletal abnormalities
- coarse face
- severe impairment
- وفاة مبكرة (~8 سنوات)



I-CELL DISEASE

- Caused by a deficiency of the ability to phosphorylate mannose.
- Characterized by skeletal abnormalities, restricted joint movement, coarse facial features, and severe psychomotor impairment.
- Death usually occurs by age eight years.

ما يخص للمرض