Glycosaminoglycans

glucose + Amino group + long chain

Glycosaminoglycans

highly negative

Attract wate

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

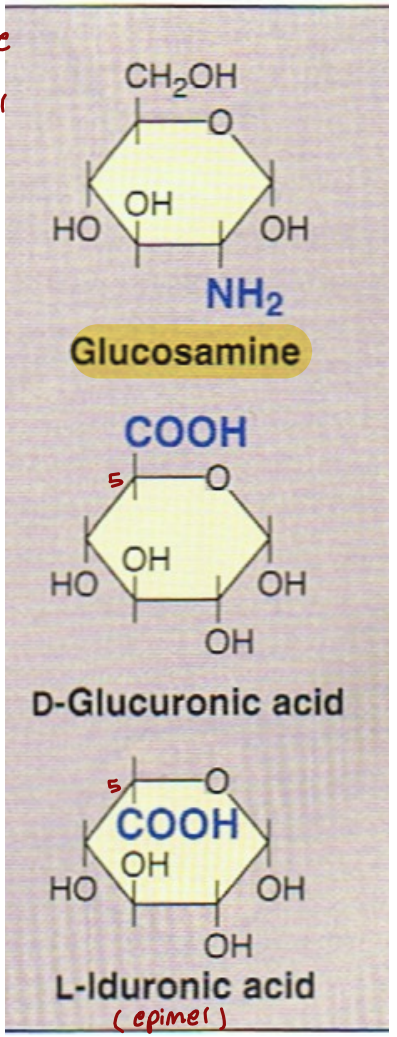
A single exception is keratan sulfate, which contains galactose rather than an acidic sugar.

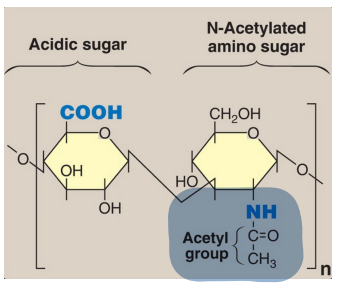
- The amino sugar is either D-glucosamine or D-galactosamine in which the amino group is usually acetylated, thus eliminating its positive charge

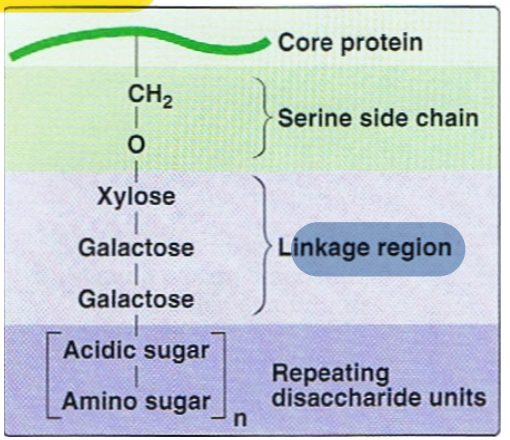
to increase negativity

- 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.







Component	Options / Details	Key Role
Amino Sugar	D-glucosamine or D-galactosamine	Often acetylated or sulfated
Acidic Sugar	D-glucuronic or L-iduronic acid (carbon 5 epimer)	Provides negative charge
Linkage Region	Xylose - Galactose - Galactose	Connects GAG to Core Protein
Attachment Point	Serine side chain	The "hook" on the protein

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**.

  mucous

- As essential components of cell surfaces, GAGs play an important role in **mediating cell-cell signaling** and **adhesion**

Property	Result in the Body
Water Binding	Creates a gel-like matrix (Ground Substance)
Viscosity	Lubricates mucous membranes
Surface Presence	Mediates signaling and cell adhesion

Classes of GAGs

- There are six major classes of glycosaminoglycans, including:
  - chondroitin 4- and 6-sulfates
  - keratan sulfate
  - dermatan sulfate
  - Heparin
  - heparan sulfate
  - hyaluronic acid.

1. **Chondroitin 4- and 6-sulfates:** The most abundant GAGs in the body.
2. **Keratan sulfate:** Unique because it is the only one that **does not contain an uronic acid**.
3. **Dermatan sulfate:** Found in skin and blood vessels.
4. **Heparin:** Strictly **intracellular** (found inside mast cells).
5. **Heparan sulfate:** Found on cell surfaces and basement membranes.
6. **Hyaluronic acid:** The "odd one out" for two reasons: it is **not sulfated** and **not covalently attached to a protein**.

- 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

protein + GAGs chains (covalently)

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

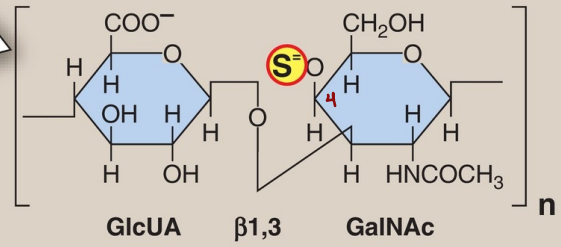
Feature	Hyaluronic Acid	All Other GAGs
Sulfated?	No	Yes
Attached to Protein? covalently??	No (forms the "spine" of aggregates) attach to core protein non covently	Yes (covalently attached to core protein)
Location	Extracellular	Extracellular (except Heparin) intracellular

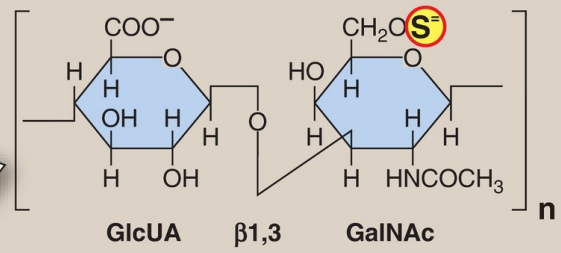
* hyaluronic acid attach to core protein non covalently

very important :

CHONDROITIN 4- AND 6-SULFATES

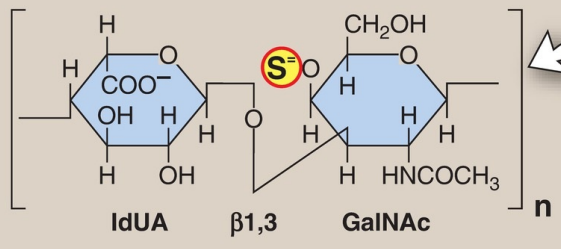
- Disaccharide unit: N-acetylgalactosamine with Ⓢ on either carbon (C) 4 or C 6 and glucuronic acid
- **Most abundant GAG in the body**
- Found in cartilage, tendons, ligaments, and aorta
- Form proteoglycan aggregates, through noncovalent association with hyaluronic acid
- In cartilage, bind collagen and hold fibers in a tight, strong network





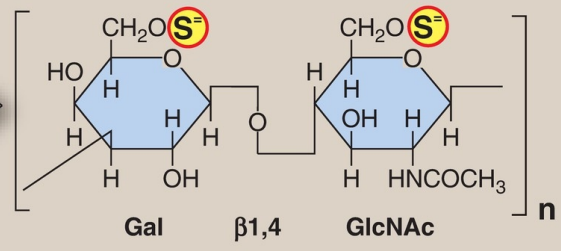
DERMATAN SULFATE

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



KERATAN SULFATES (KS) I and II

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

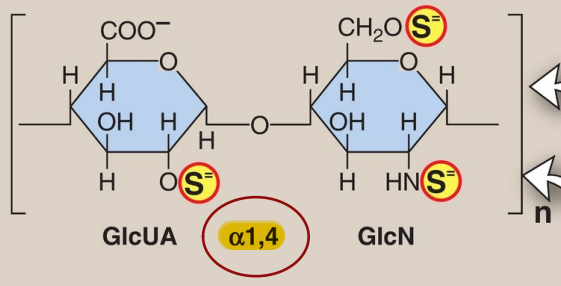


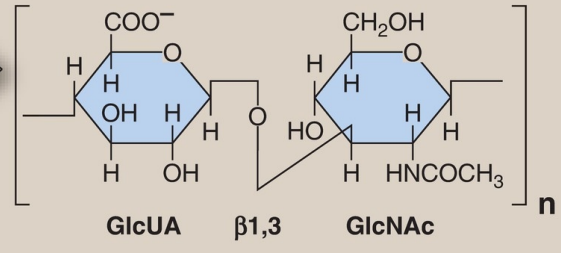
HEPARIN

- 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 Ⓢ per disaccharide unit)
- **α-Linkage joins the sugars**
- Unlike other GAG 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** ★

HYALURONIC ACID

- Disaccharide unit: N-acetylglucosamine and glucuronic acid
- Different from other GAG: **not sulfated, not covalently attached to protein**, and **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





HEPARAN SULFATE

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

Intracellular vs. Extracellular: Only **Heparin** is intracellular.

Uronic Acid: Only **Keratan Sulfate** lacks uronic acid.

Sulfation: Only **Hyaluronic Acid** has no sulfate.

The Linkage: Heparin and Heparan use α**-linkages**.

Which glycosaminoglycan (GAG) is composed of a repeating disaccharide unit of **N-acetylgalactosamine** and **L-iduronic acid**?

- سؤال حكتله الدكتورة بالمحاضرة -

Choices:

A) Chondroitin sulfate

B) Keratan sulfate

C) Hyaluronic acid

D) Heparin

E) **Dermatan sulfate** +4

1. Which of the following pairings between a Glycosaminoglycan (GAG) and its unique structural feature is INCORRECT?

- **A.** Hyaluronic acid — Only GAG that is non-sulfated and exists as a protein-free chain.
- **B.** Keratan sulfate — Only GAG that lacks a uronic acid and contains Galactose instead.
- **C.** Heparin — Strictly an extracellular GAG found in the synovial fluid.
- **D.** Dermatan sulfate — Defined by the presence of L-iduronic acid.
- **E.** All of the above are correct.

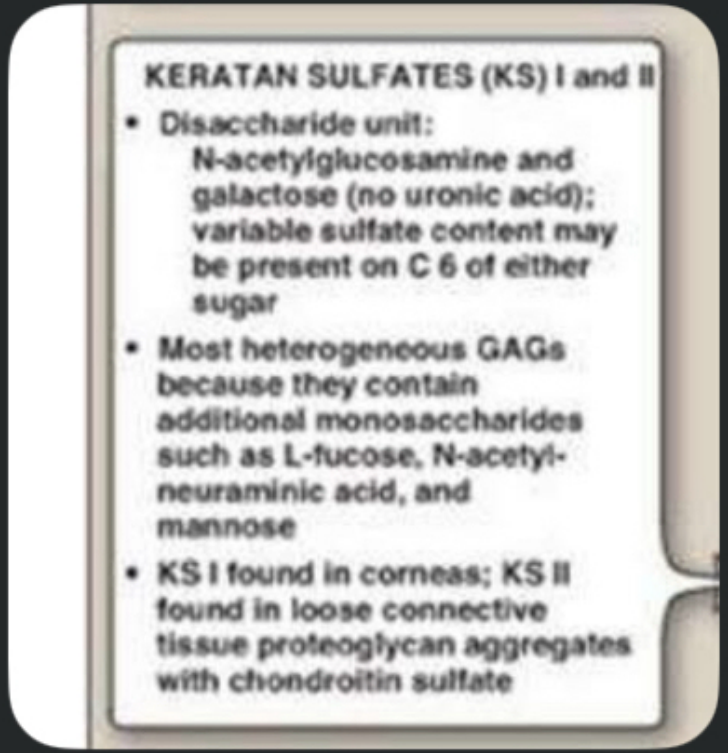
Answer: C. Heparin is unique because it is an **intracellular** GAG found in mast cells.

2. Hyaluronic acid differs from most other GAGs because it:

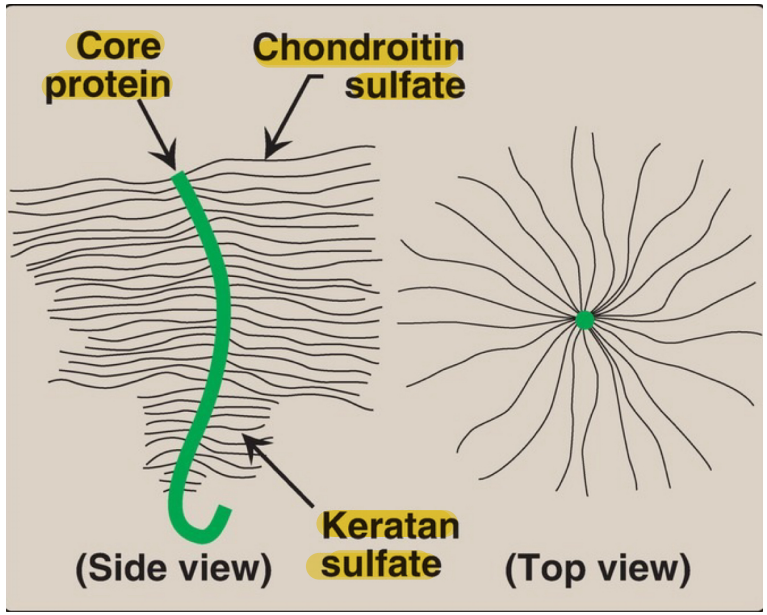
- **A.** Is synthesized in the mitochondria.
- **B.** Is not covalently attached to a core protein.
- **C.** Contains only alpha-glycosidic linkages.
- **D.** Is the only GAG found inside mast cells.
- **E.** None of the above.

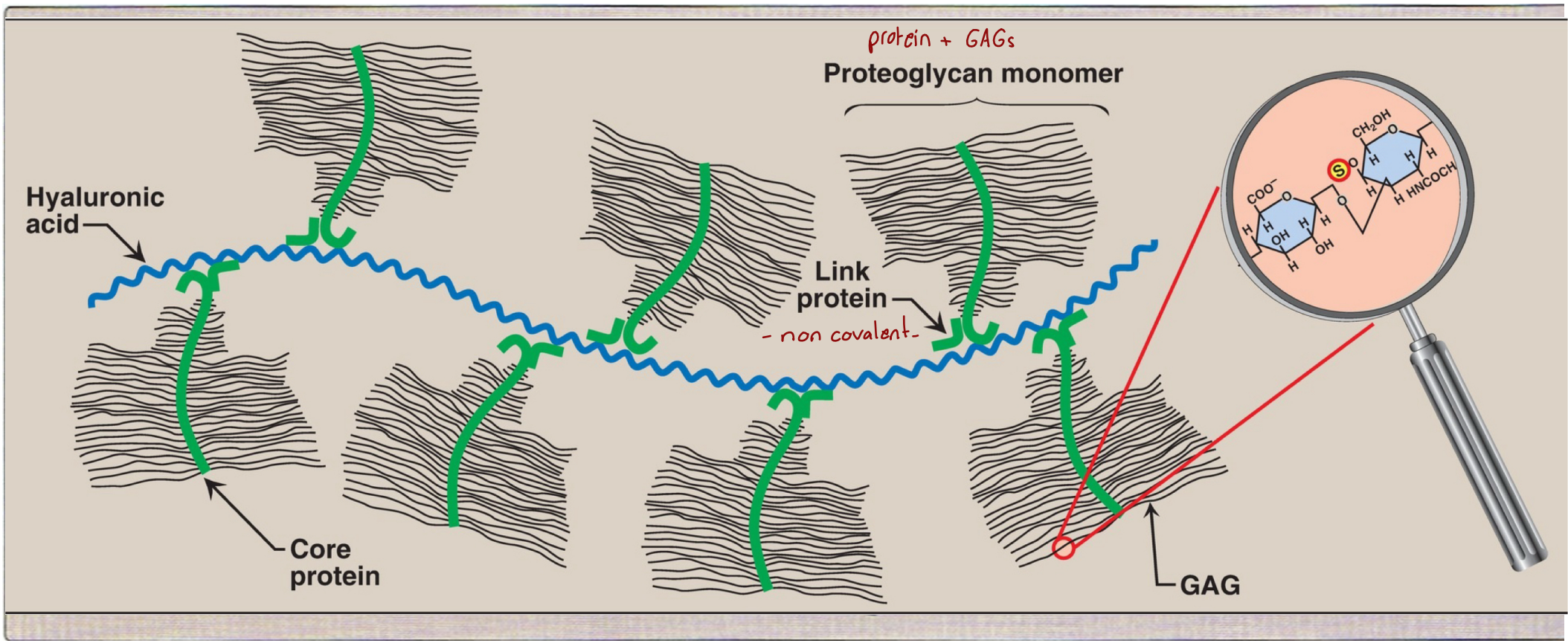
Answer: B. It associates with proteins only non-covalently.

جابت انه مين ال GAGs فش فيه uronic



انواع ال GAG ايش الخطأ
كان الجواب Keratan intracellor
او ممكن نوع ثاني المهم خطأ لانو الوحيد الانترا هو Heparin

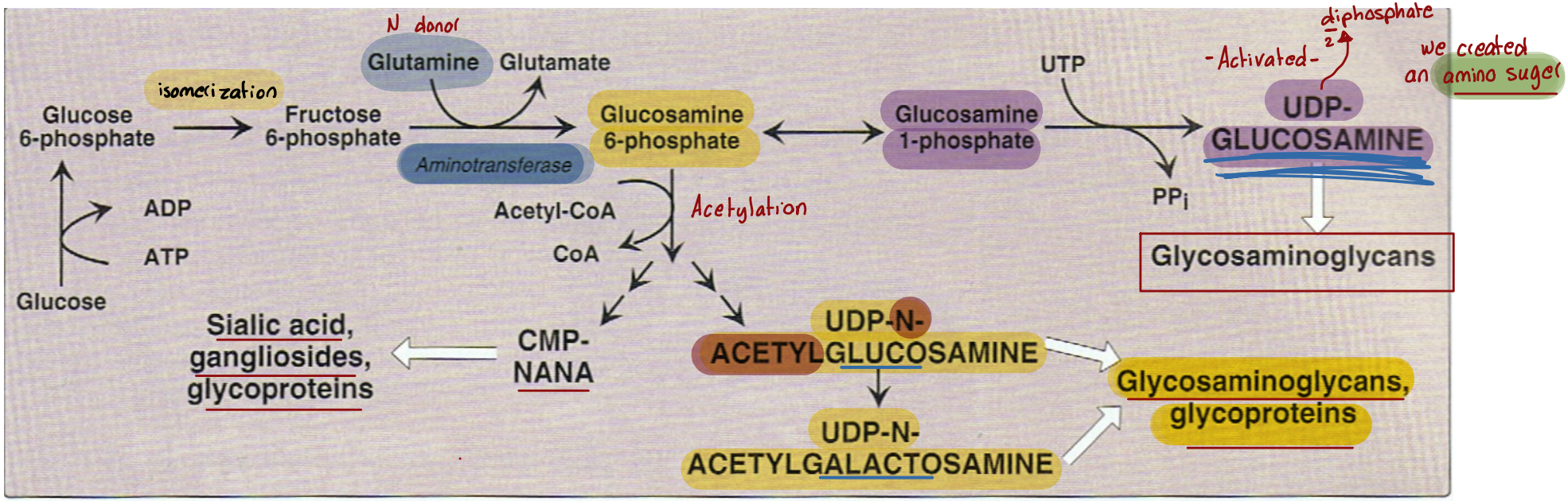

Core protein
Chondroitin sulfate
Keratan sulfate
(Side view)
(Top view)

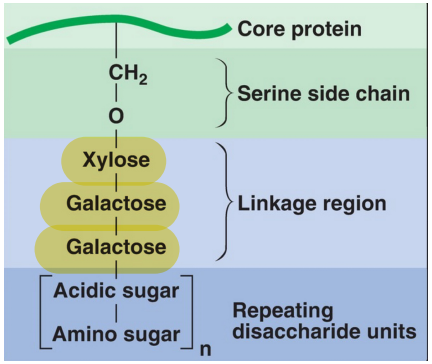

protein + GAGs
Proteoglycan monomer
Hyaluronic acid
Link protein
- non covalent-
Core protein
GAG

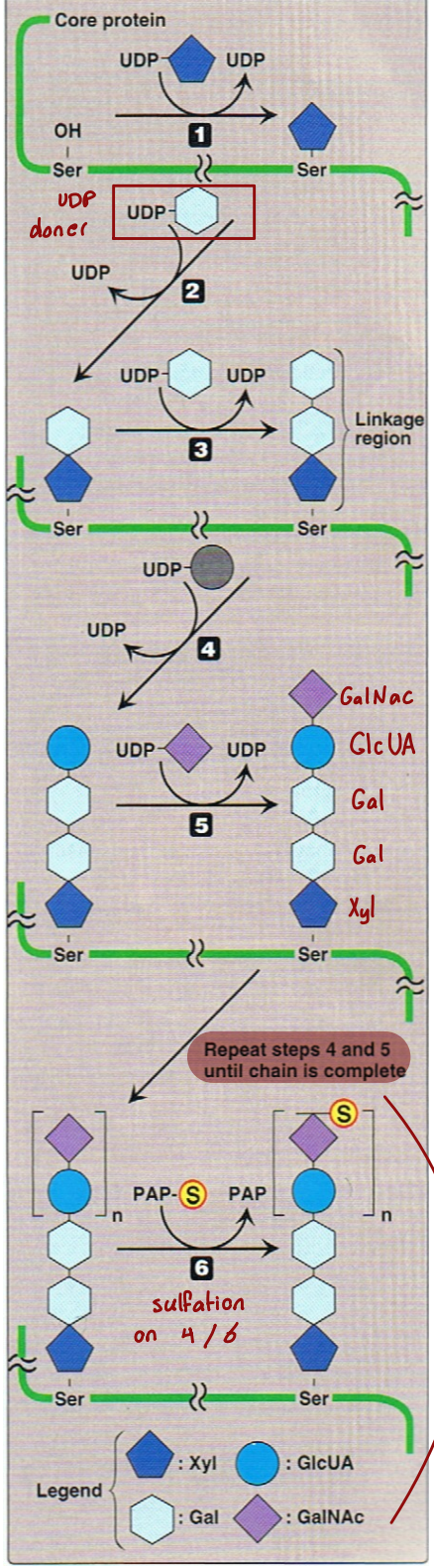
Synthesis of Glycosaminoglycans

Because GAG are produced for export from the cell, their synthesis occurs primarily in the Golgi and not in the cytosol.

- GAGs are synthesized in the endoplasmic reticulum and the Golgi
- The polysaccharide chains are elongated by the sequential addition of alternating acidic and amino sugars, donated by their UDP- derivatives
- The last step in synthesis is sulfation of some of the amino sugars. The source of the sulfate is 3'- phosphoadenosyl-5'-phosphosulfate. PAPS







كلهم يعملوا على الخطوة ما عدا hyaluronic acid

Mucopolysaccharidosis

mucous

مرض GAGS ↑ كمية

الإنزيمات قلت

1- mental retardation تخلف عقلي

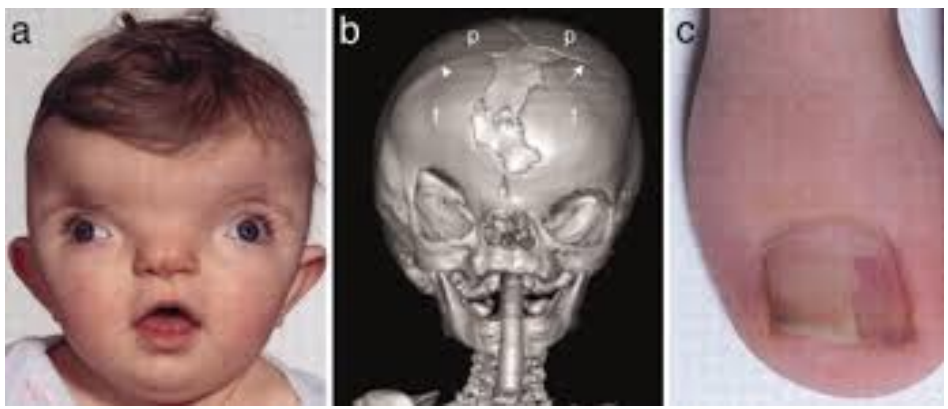
2- skeletal + extracellular matrix deformities.

- 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 mucopoly-saccharidosis.

- These are hereditary disorders in which glycosaminoglycans accumulate in tissues, causing symptoms such as ① skeletal and extracellular matrix deformities, and ② mental retardation

- Examples of these genetic diseases include Hunter and Hurler syndromes



8. Regarding the degradation of GAGs, which statement is INCORRECT?

- **A.** Degradation occurs primarily within the lysosomes by [redacted] lysosomal hydrolases.
- **B.** Chains are broken down sequentially starting from the reducing end.
- **C.** Hunter and Hurler syndromes are examples of Mucopolysaccharidoses.
- **D.** Deficiency in a single enzyme stops the whole degradation line.
- **E.** All are correct.

Answer: B. Degradation starts from the **non-reducing** end.

protein sugars

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)
  (2-10)

- The carbohydrates of glycoproteins **do not have serial repeats** as do glycosaminoglycans.

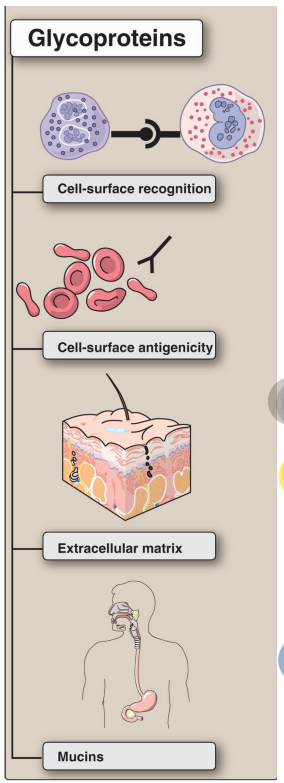
Feature	Proteoglycans	Glycoproteins
Carbohydrate Content	Very high (up to 95%)	Much lower
Chain Length	Long, linear chains (GAGs)	Short chains (Oligosaccharides) (2-10)
Structure	Unbranched (linear)	Often highly branched
Repeating Units	Serial repeating disaccharides	No serial repeats
Sugar Count	Hundreds of sugar residues	Typically 2 to 10 residues

protein is major

Function of glycoproteins

موجود في
- ECM
- mucins in the GI and urogential tract

➢ Membrane-bound glycoproteins participate in a broad range of cellular phenomena, including:



خلوا اخر

Cell surface recognition (by other cells, hormones, viruses)

Cell surface antigenicity (such as the blood group antigens)

ABO

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.

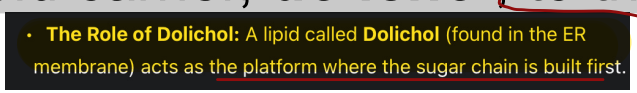
Synthesis of Glycoproteins

- Glycoproteins are synthesized in the endoplasmic reticulum and the Golgi. ⇒ secretion outside the cell

- 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

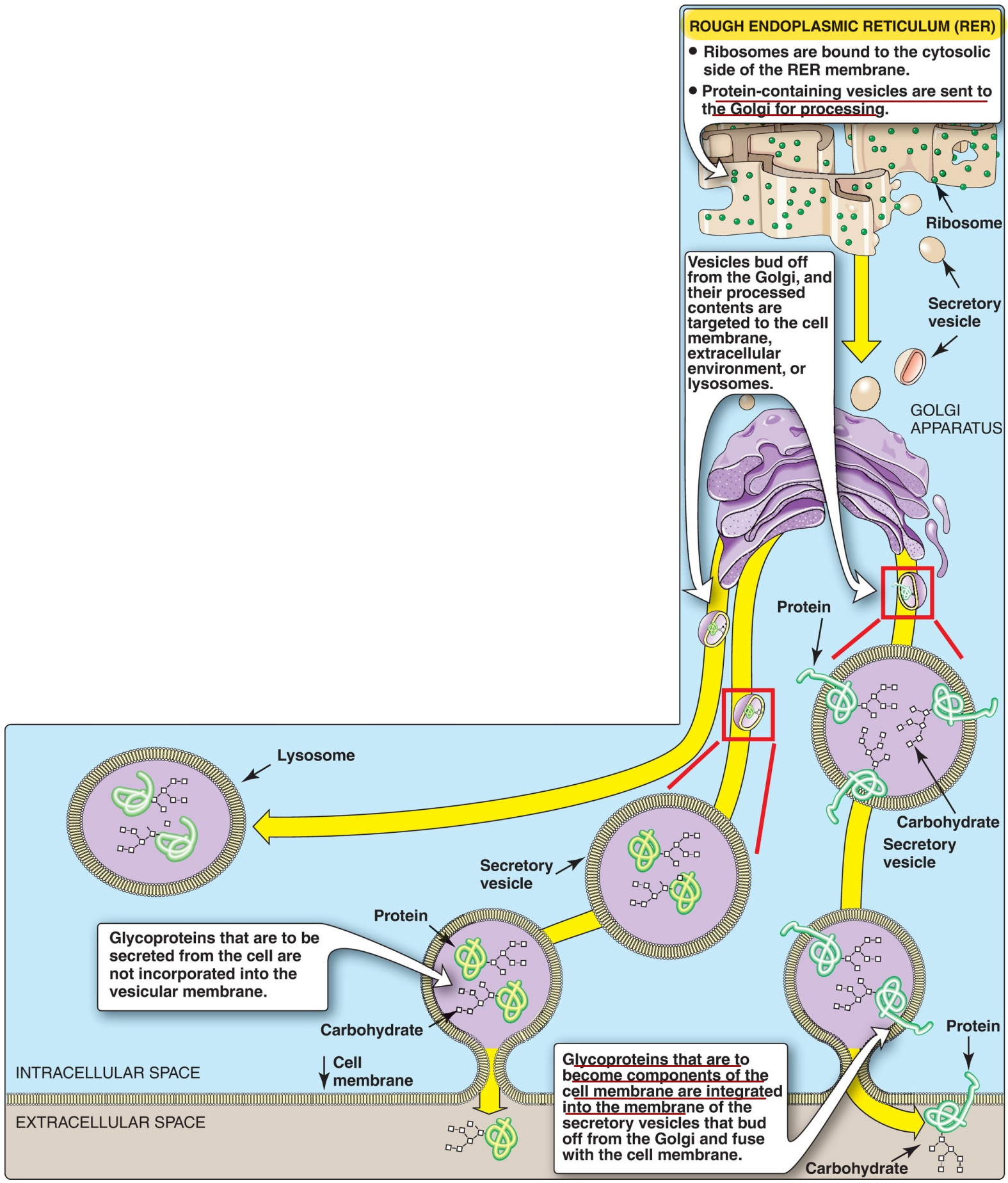
- N-linked glycoproteins contain varying amounts of mannose. They are synthesized by the transfer of a pre-formed oligosaccharide from its membrane lipid carrier, **dolichol**, to the protein



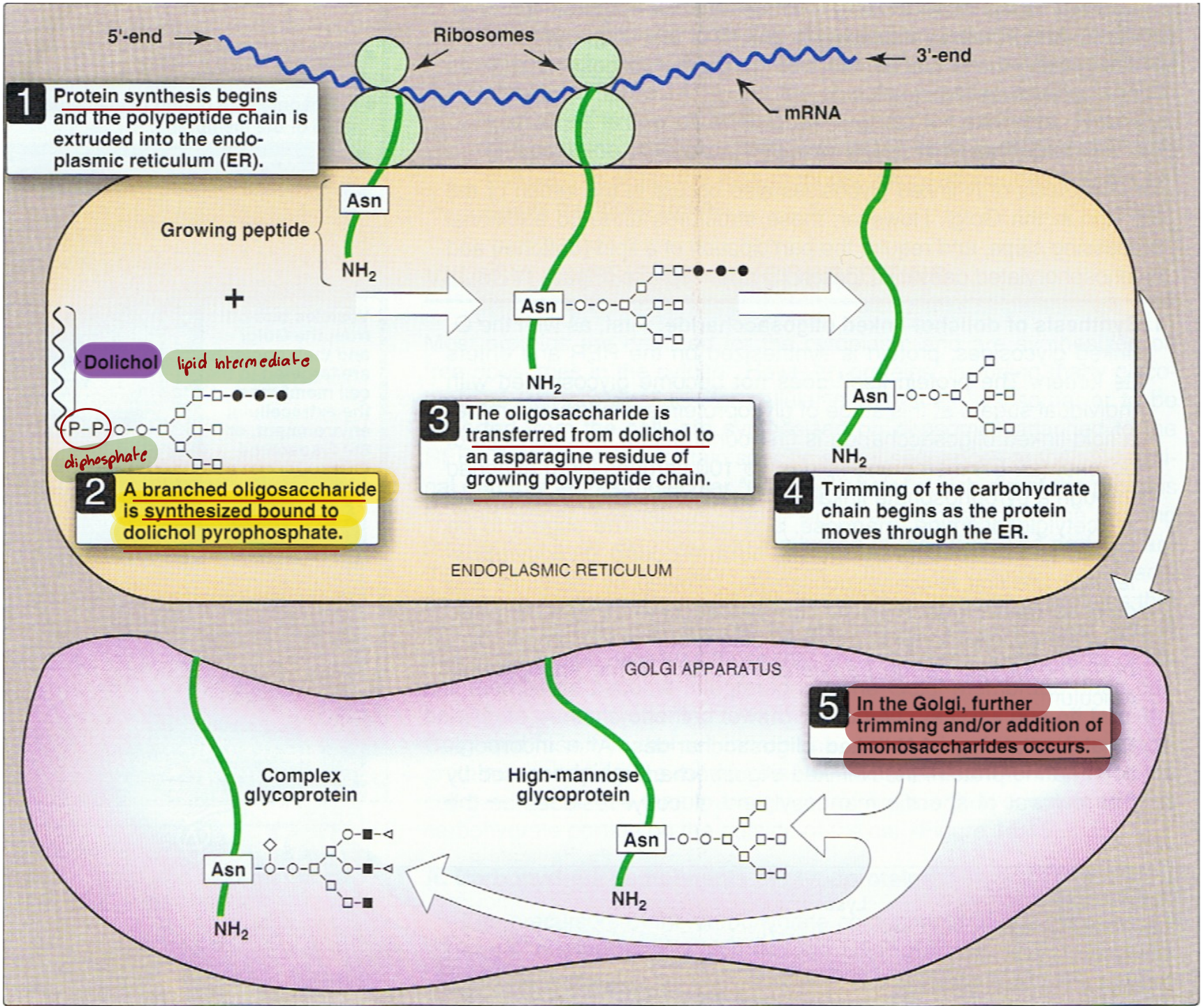
oils
2 phosphate

- They also require **dolichol**, an intermediate carrier of the growing oligosaccharide chain.

Feature	O-linked Glycoproteins	N-linked Glycoproteins
Attachment Site	Attached to the Hydroxyl (-OH) group of Serine or Threonine.	Attached to the Amide nitrogen ($-NH_2$) of Asparagine.
Sugar Sequence	No specific consensus sequence; enzymes recognize the protein's secondary structure.	Requires a specific consensus sequence: Asn-X-Ser/Thr (where X is any amino acid except proline).
Synthesis Method	Step-by-step: Sugars are added one at a time directly to the protein.	En bloc: A pre-formed oligosaccharide is transferred all at once to the protein.
Lipid Carrier	None; built directly on the protein.	Uses Dolichol (a membrane lipid) as a temporary platform.
Location	Occurs primarily in the Golgi apparatus.	Starts in the RER (assembly and transfer) and finishes in the Golgi (trimming/processing).
Composition	Short, often linear or simple branched chains.	Highly branched; divided into Complex or High-mannose types.


ROUGH ENDOPLASMIC RETICULUM (RER)
• Ribosomes are bound to the cytosolic side of the RER membrane.
• Protein-containing vesicles are sent to the Golgi for processing.
Ribosome
Vesicles bud off from the Golgi, and their processed contents are targeted to the cell membrane, extracellular environment, or lysosomes.
Secretory vesicle
GOLGI APPARATUS
Protein
Lysosome
Carbohydrate
Secretory vesicle
Secretory vesicle
Protein
Glycoproteins that are to be secreted from the cell are not incorporated into the vesicular membrane.
Carbohydrate
Protein
INTRACELLULAR SPACE
Cell membrane
Glycoproteins that are to become components of the cell membrane are integrated into the membrane of the secretory vesicles that bud off from the Golgi and fuse with the cell membrane.
EXTRACELLULAR SPACE
Carbohydrate

Synthesis of N-linked glycoproteins.



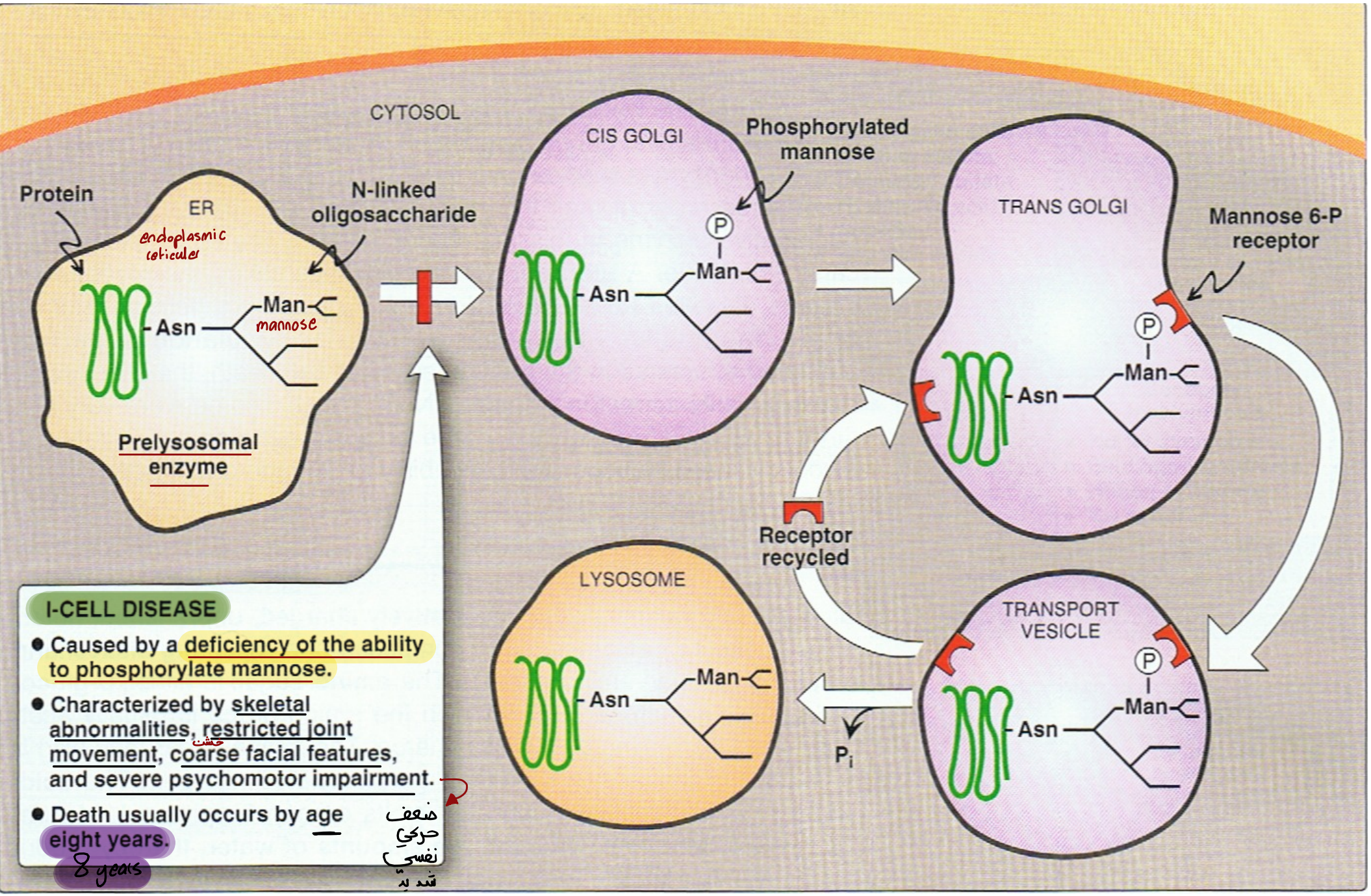
Lysosomal degradation of glycoproteins

بعد ما يخلصوا وظيفتهم

- 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

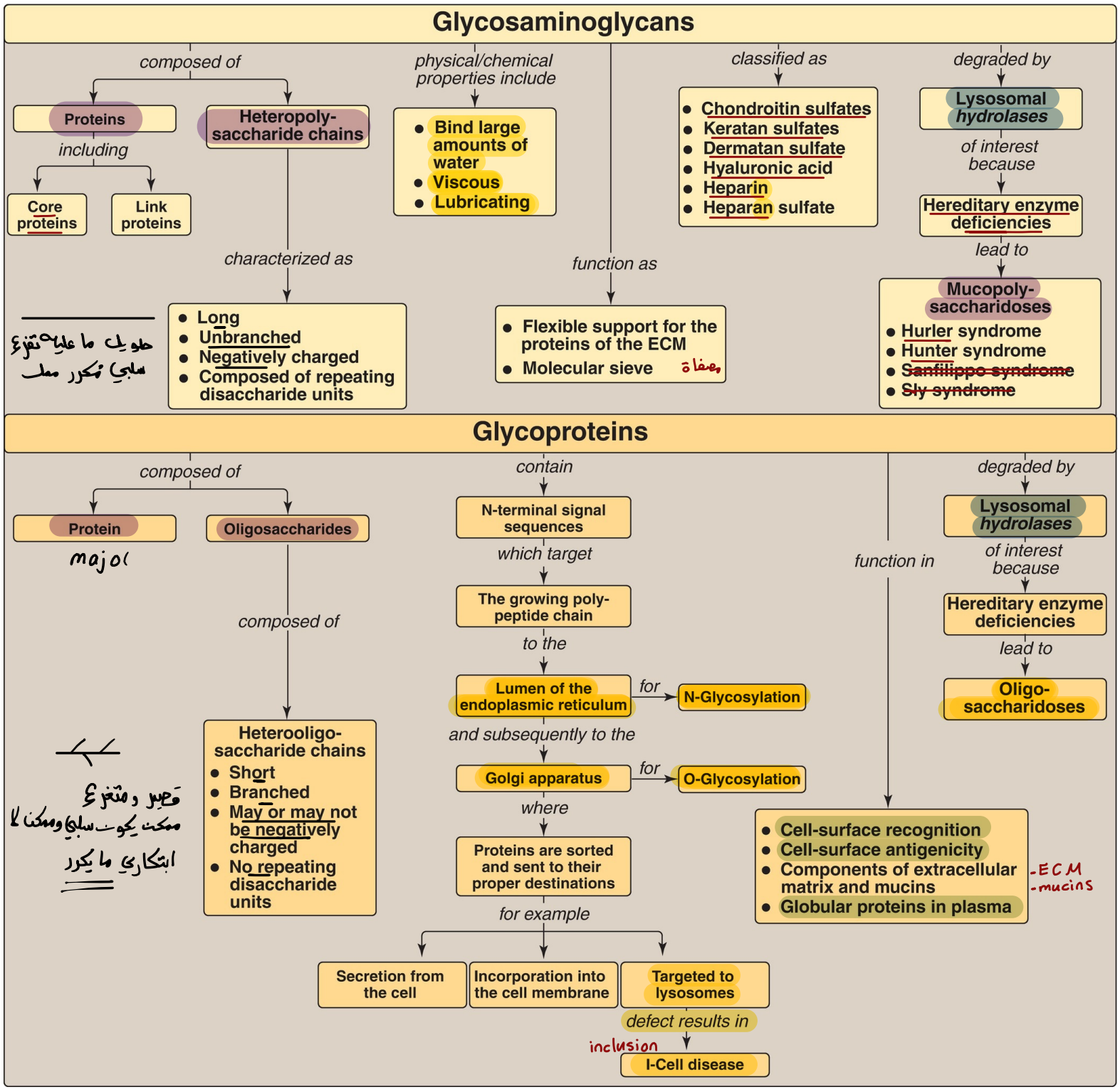


I-CELL DISEASE

- Caused by a deficiency of the ability to phosphorylate mannose.
- Characterized by skeletal abnormalities, restricted joint movement (حشت), coarse facial features, and severe psychomotor impairment.
- Death usually occurs by age eight years. (8 years)

ضعف حركي نفسي شديد

- تلخيص رهيب -



Study Questions

Choose the ONE best answer.

4.1. Mucopolysaccharidoses are hereditary lysosomal storage diseases. They are caused by:

A. defects in the degradation of glycosaminoglycans.

B. defects in the targeting of enzymes to lysosomes.

C. an increased rate of synthesis of the carbohydrate component of proteoglycans.

D. an insufficient rate of synthesis of proteolytic enzymes.

E. the synthesis of abnormally small amounts of core proteins.

F. the synthesis of heteropolysaccharides with an altered structure.

Correct answer = A. The mucopolysaccharidoses are caused by deficiencies in any one of the lysosomal acid hydrolases responsible for the degradation of glycosaminoglycans (not proteins). The enzyme is correctly targeted to the lysosome, so blood levels of the enzyme do not increase, but it is nonfunctional. In these diseases, synthesis of the protein and carbohydrate components of proteoglycans is unaffected, in terms of both structure and amount.