Lippincott® Illustrated Reviews: Biochemistry, 8e ›

Chapter Contents

14: Glycosaminoglycans, Proteoglycans, and Glycoproteins

Glycosaminoglycan Overview

Listen

Glycosaminoglycans (GAGs) are large complexes of negatively charged heteropolysaccharide chains. They are generally associated with a small amount of protein-forming structures known as *proteoglycans*, which typically consist of up to 95% carbohydrate. GAGs have the special ability to bind large amounts of water, producing the gel-like matrix that forms the basis of the body's ground substance, which, along with fibrous structural proteins such as collagen, elastin, and fibrillin-1, and adhesive proteins such as fibronectin, makes up the extracellular matrix (ECM). [a]Hydrated GAGs serve as a flexible support for the ECM, interacting with the structural and adhesive proteins, and as a molecular sieve, influencing movement of materials through the ECM. The viscous, lubricating properties of mucous secretions also result from the presence of GAGs, which led to the original naming of these compounds as mucopolysaccharides.

[a]For more information on ECM, see *LIR Cell and Molecular Biology*, 2nd Edition, Chapter 2.

Structure

Listen

GAGs are long, unbranched, heteropolysaccharide composed of repeating disaccharide chains where one of the sugars is an *N*-acetylated amino sugar, either *N*-acetylglucosamine (GlcNAc) or *N*-acetylgalactosamine (GalNAc) (Fig. 14.1), and the other is an acidic sugar. 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, eliminating its positive charge. 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 C-5 epimer L-iduronic acid (Fig. 14.2). These uronic sugars contain carboxyl groups that are negatively charged at physiologic pH and, together with the sulfate groups ($-SO_4^{2-}$), give GAGs their strongly negative nature.

FIGURE 14.1

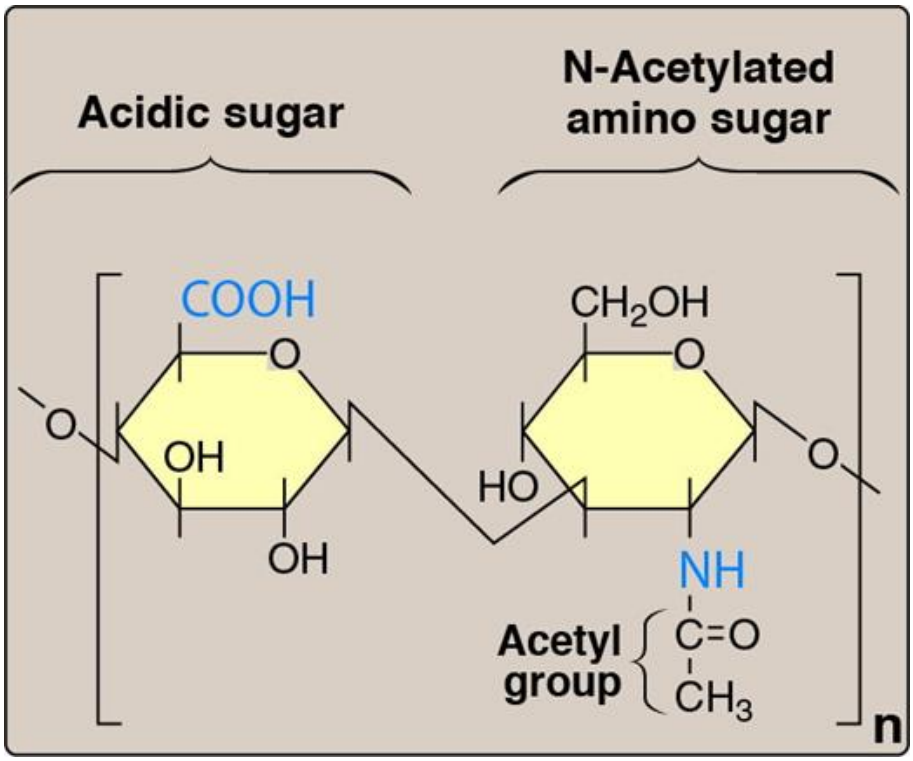
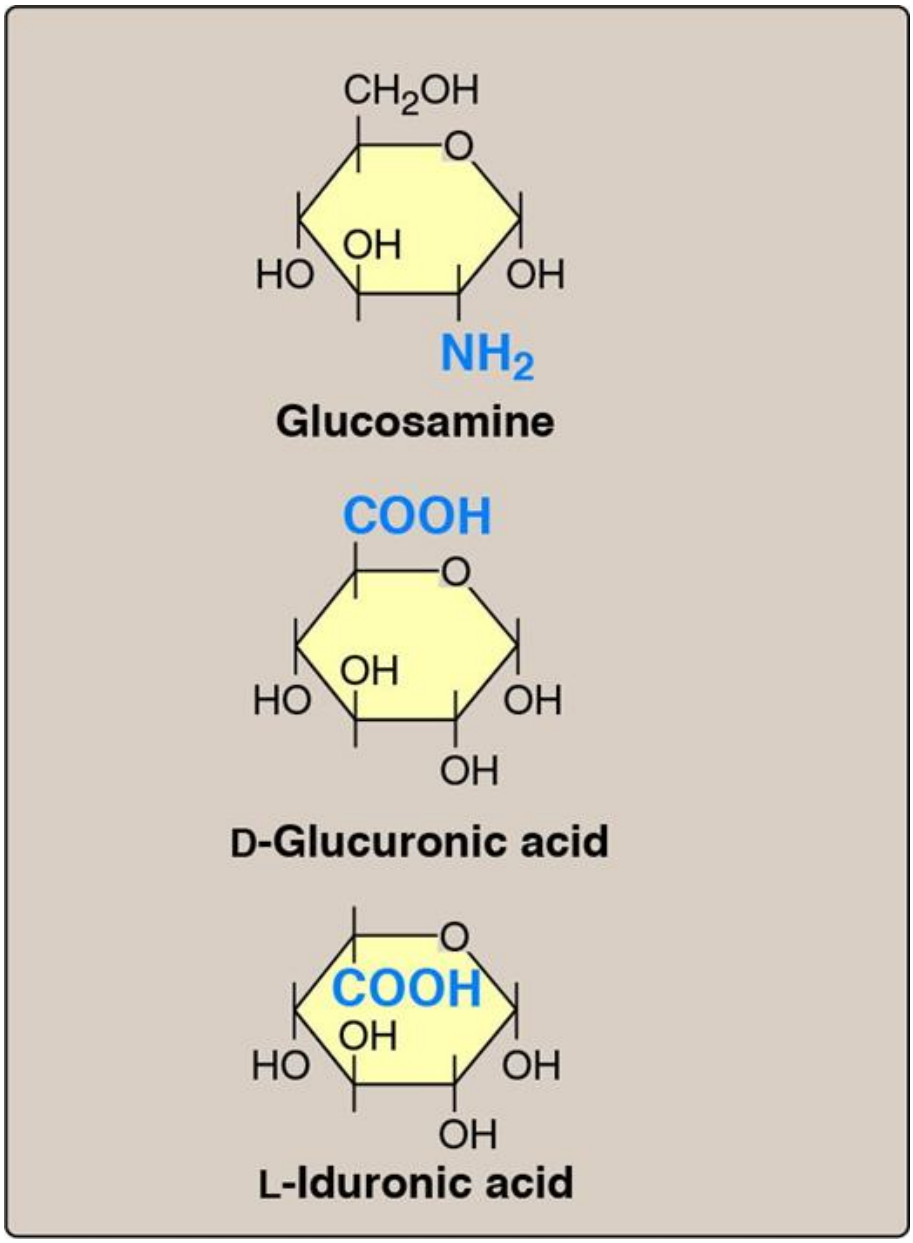

Acidic sugar
N-Acetylated amino sugar
COOH
O
OH
OH
O
CH2OH
O
HO
O
NH
Acetyl group
C=O
CH3
n

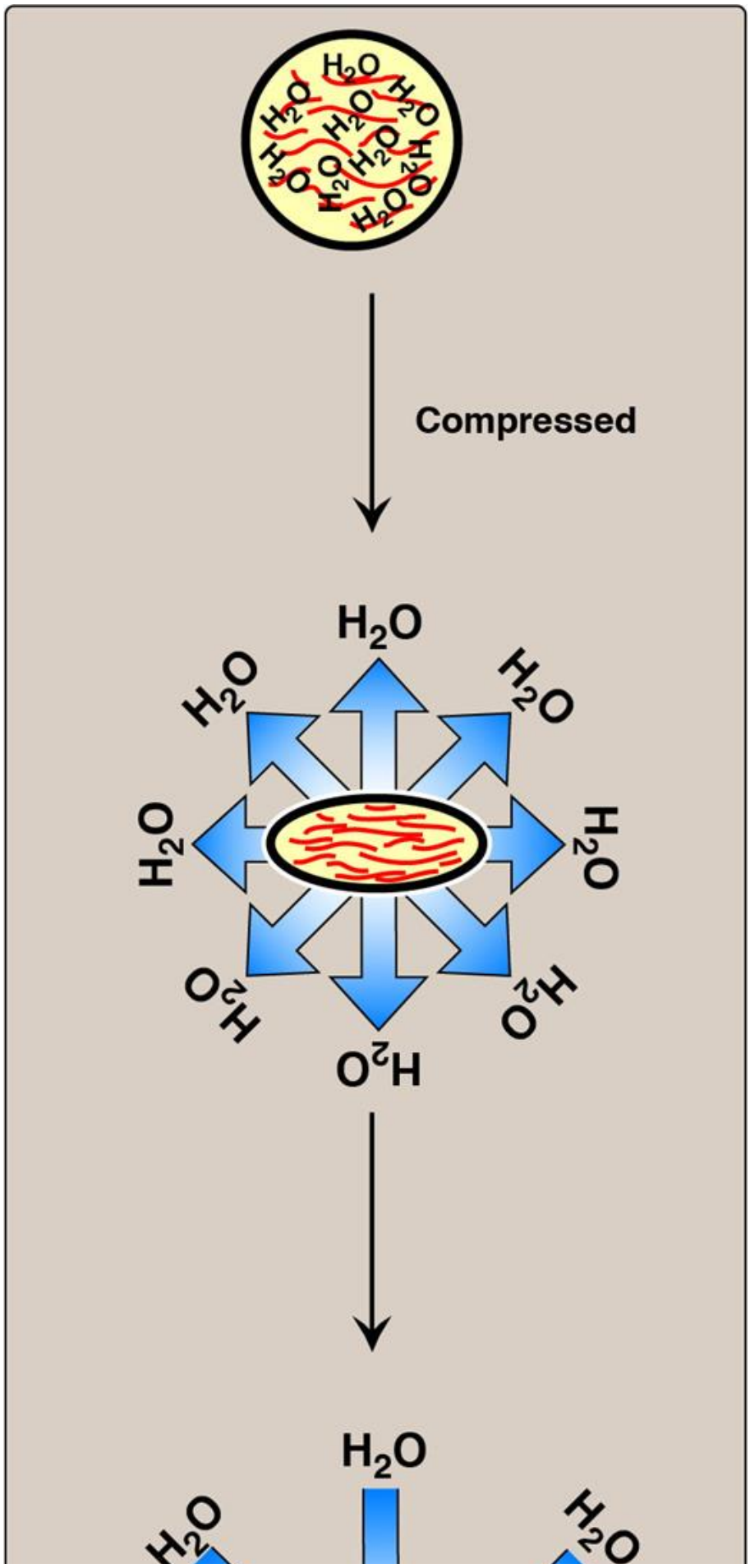
FIGURE 14.2

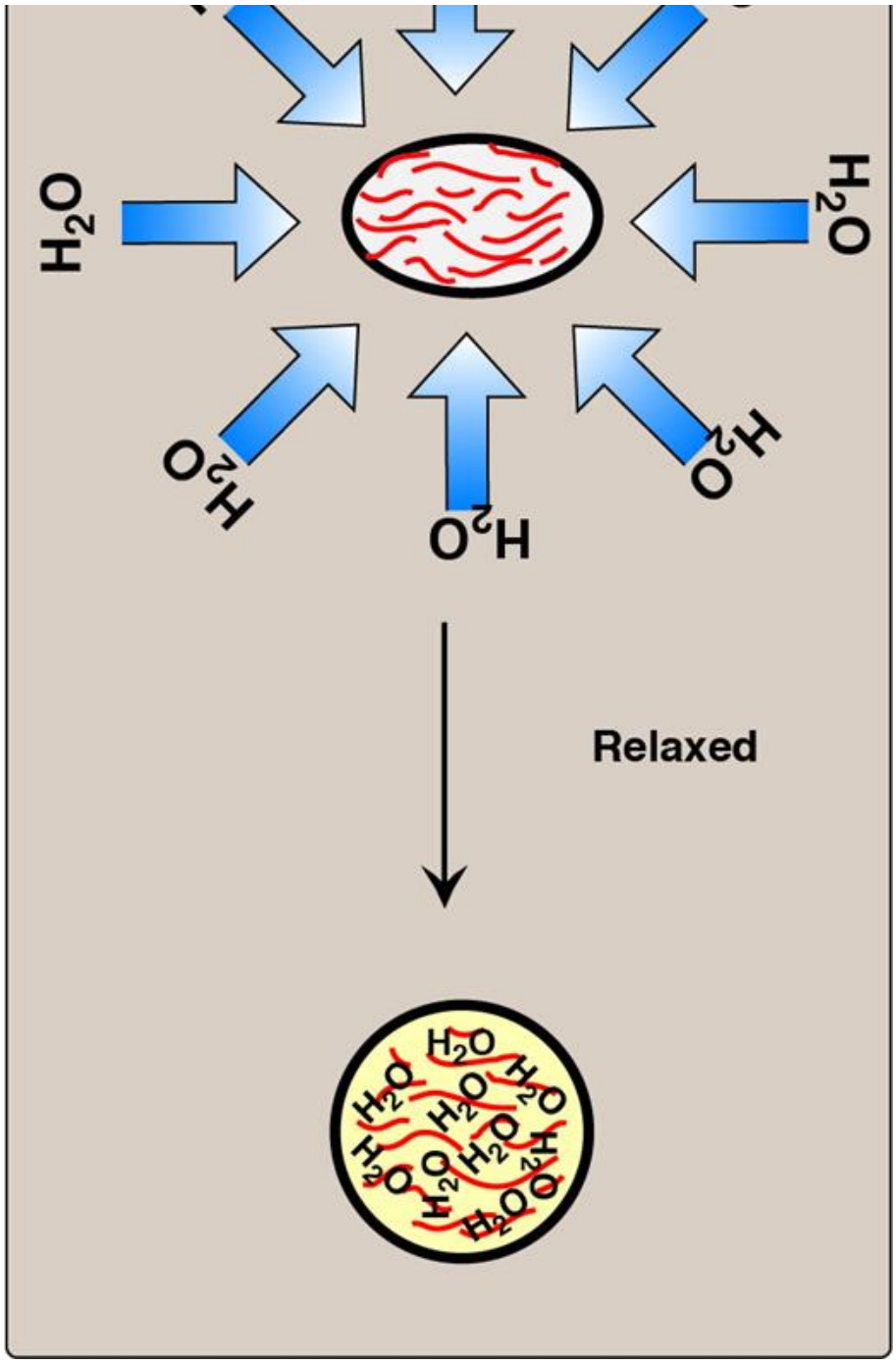


Structure–function relationship

Because of the high concentration of negative charges, these repeating disaccharide chains tend to be extended in solution. They repel each other and are surrounded by a shell of water molecules. When brought together, they slide past each other, much as two magnets with the same polarity seem to slide past each other. This produces the slippery consistency of mucous secretions and synovial fluid. When a solution containing GAGs is compressed, the water is squeezed out, and the GAGs are forced to occupy a smaller volume. When the compression is released, the GAGs spring back to their original, hydrated volume because of the repulsion of their negative charges. This property contributes to the resilience of cartilage, synovial fluid, and the vitreous humor of the eye (Fig. 14.3).

FIGURE 14.3

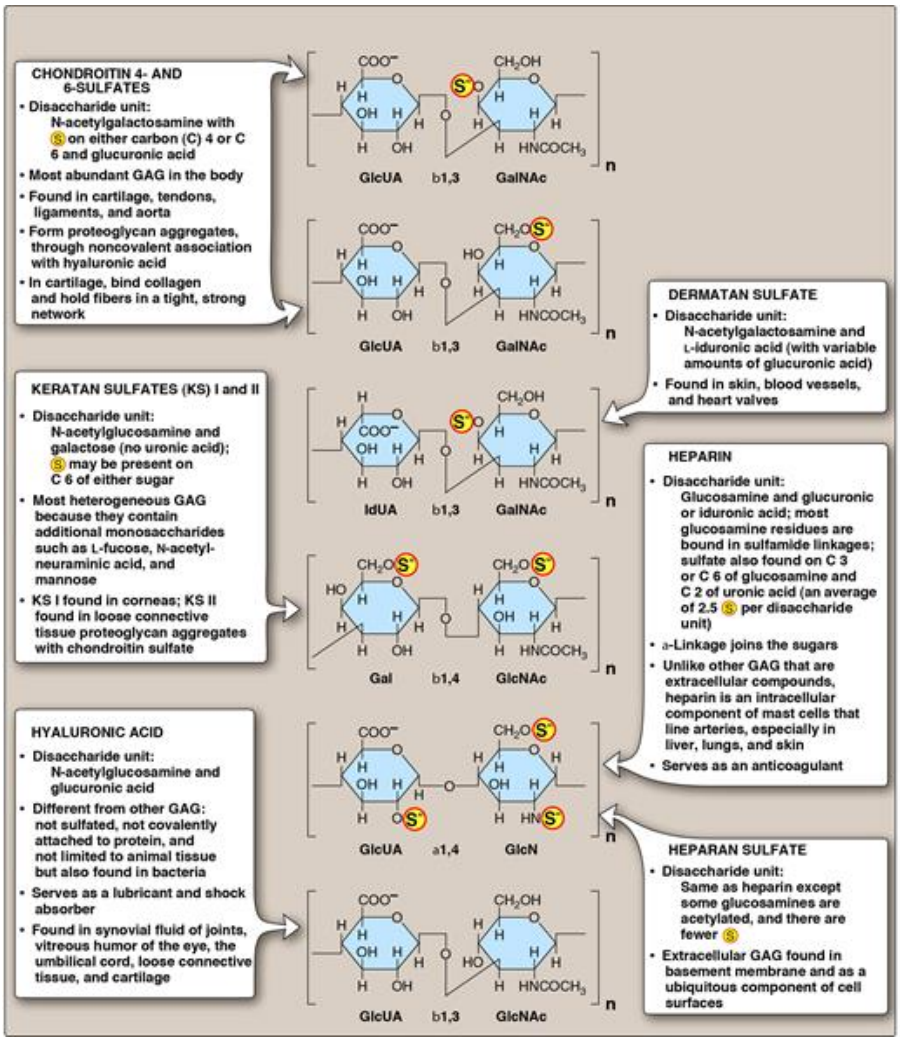




Classification

The six major types of GAGs are divided according to monomeric composition, type of glycosidic linkages, and degree and location of sulfate units. The structure of the GAGs and their distribution in the body is illustrated in Figure 14.4. All GAGs, except for hyaluronic acid, are sulfated and are found covalently attached to protein, forming proteoglycan monomers.

FIGURE 14.4



lycans (GAGs).

= glucuronic and iduronic acids; glucosamine; Gal = galactose.

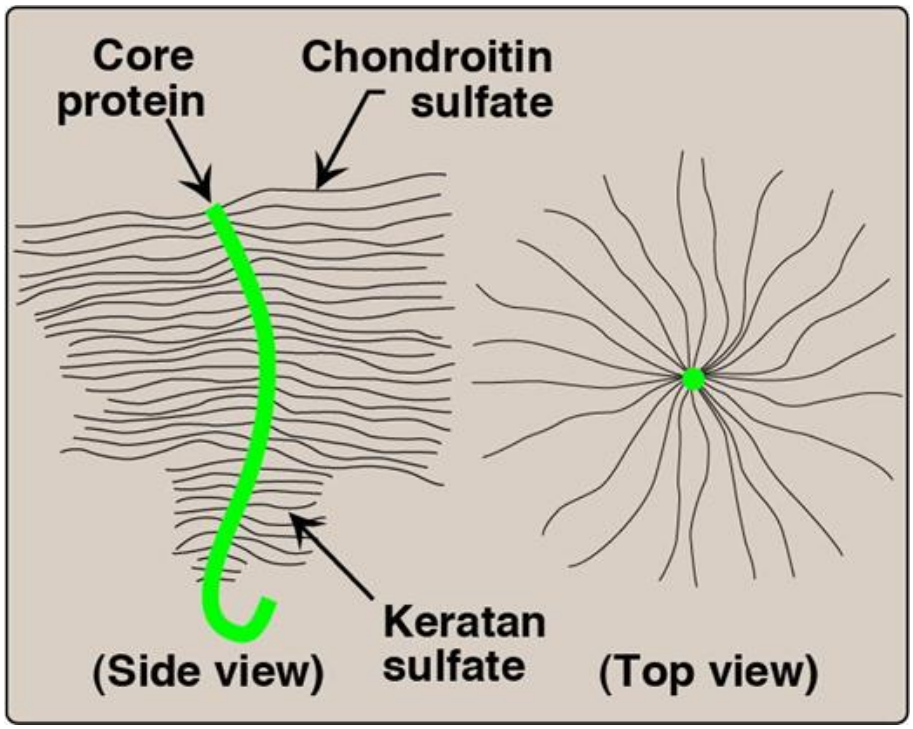
Proteoglycans

Proteoglycans are found in the ECM and on the outer surface of cells.

Monomer structure

A proteoglycan monomer found in cartilage consists of a core protein to which up to 100 linear chains of GAGs are covalently attached. These chains, which may each be composed of up to 200 disaccharide units, extend out from the core protein and remain separated from each other because of charge repulsion. The resulting structure resembles a bottle brush (Fig. 14.5). In cartilage proteoglycans, chondroitin sulfate and keratan sulfate are the main types of GAGs. Note that proteoglycans are grouped into gene families that encode core proteins with common structural features. The aggrecan family (aggrecan, versican, neurocan, and brevican), abundant in cartilage, is an example.

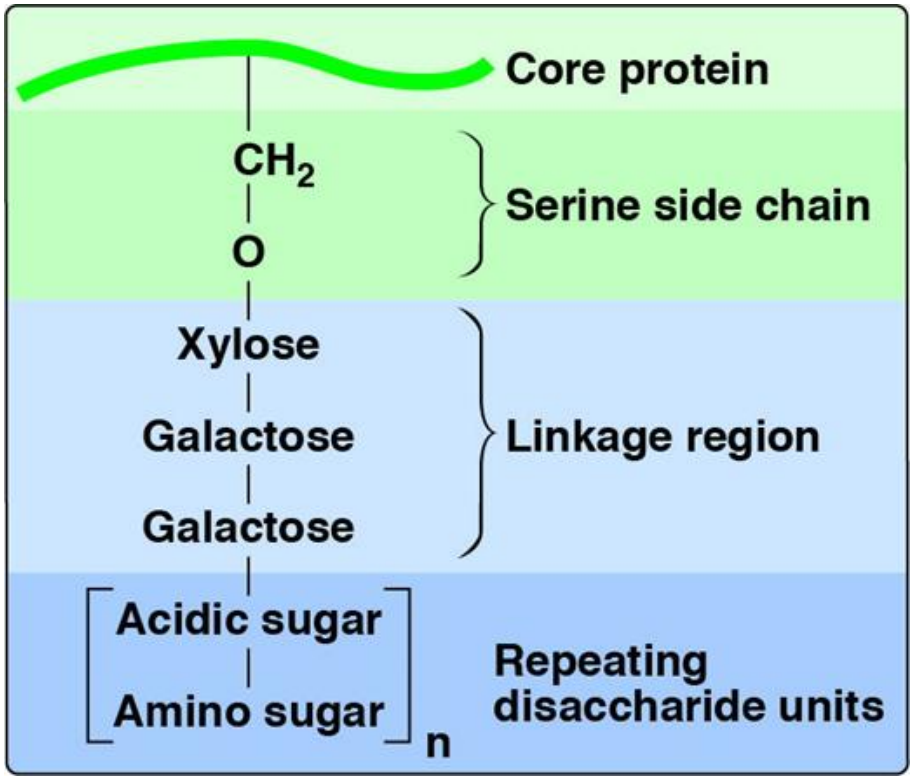
FIGURE 14.5



GAGs–protein linkage

GAGs attached to core protein via covalent linkage are most commonly through a trihexoside (galactose–galactose–xylose) and a serine residue in the protein. An O-glycosidic bond is formed between the xylose and the hydroxyl group of the serine (Fig. 14.6).

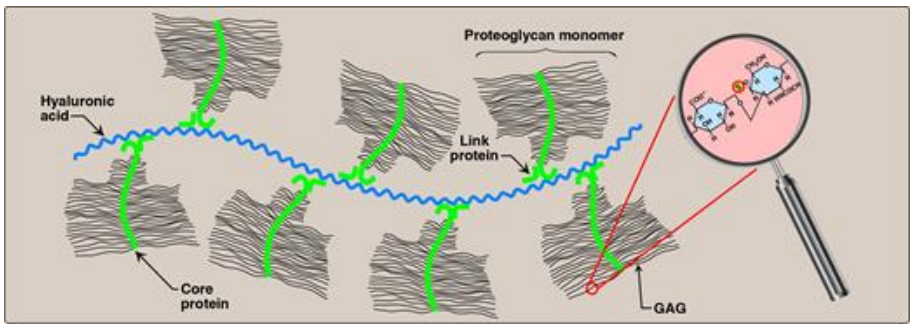
FIGURE 14.6



Aggregate formation

Many proteoglycan monomers can associate with one molecule of hyaluronic acid to form proteoglycan aggregates. The association is not covalent and occurs primarily through ionic interactions between the core protein and the hyaluronic acid. The association is stabilized by additional small proteins called link proteins (Fig. 14.7).

FIGURE 14.7



CLINICAL APPLICATION 14.1

Proteoglycans, Cartilage, and Osteoarthritis

Osteoarthritis affects millions of individuals worldwide. In this disease, joint cartilage is degraded and proteoglycans that normally help provide a cushion for the joint are lost. Without the resilience of the cartilage protecting the joint, there is pain, stiffness, and swelling, with progressive worsening of signs and symptoms. Glucosamine and chondroitin have been reported both to relieve pain and to stop progression of osteoarthritis. These compounds are readily available as over-the-counter dietary supplements in the United States. Based on several well-controlled clinical studies, it appears that glucosamine sulfate (but not glucosamine hydrochloride) and chondroitin sulfate may have a small to moderate effect in relieving symptoms of osteoarthritis.

Synthesis

Listen

The heteropolysaccharide chains are elongated by the sequential addition of alternating acidic and amino sugars donated primarily by their uridine diphosphate (UDP) derivatives. The reactions are catalyzed by a family of specific glycosyltransferases. Because GAGs are produced for export from the cell, their synthesis occurs primarily in the Golgi.

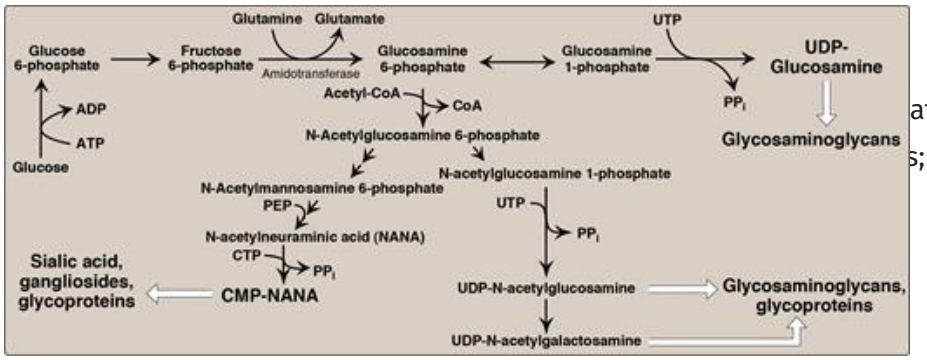
Amino sugar synthesis

Amino sugars are essential components of glycoconjugates such as proteoglycans, glycoproteins, and glycolipids. The synthetic pathway of amino sugars (hexosamines) is very active in connective tissues, where as much as 20% of glucose flows through this pathway.

N-Acetylglucosamine and N-acetylgalactosamine

The monosaccharide fructose 6-phosphate is the precursor of GlcNAc and GalNAc. A hydroxyl group on the fructose is replaced by the amide nitrogen of a glutamine, and the glucosamine 6-phosphate product gets acetylated, isomerized, and activated, producing the nucleotide sugar UDP-GlcNAc (Fig. 14.8). UDP-GalNAc is generated by the epimerization of UDP-GlcNAc. It is these nucleotide sugar forms of the amino sugars that are used to elongate the carbohydrate chains.

FIGURE 14.8



ates; CoA = coenzyme A; PEP = s; PP_i = pyrophosphate.

N-Acetylneuraminic acid

NANA, a nine-carbon, acidic monosaccharide (see Fig. 17.15), is a member of the family of sialic acids, each of which is acylated at a different site. These compounds are usually found as terminal carbohydrate residues of oligosaccharide side chains of glycoproteins, of glycolipids, or, less frequently, of GAGs. N-Acetylmannosamine 6-phosphate (derived from fructose 6-phosphate) and phosphoenolpyruvate (an intermediate in glycolysis) are the immediate sources of the carbons and nitrogens for NANA synthesis (see Fig. 14.8). Before NANA can be added to a growing oligosaccharide, it must be activated to cytidine monophosphate (CMP)-NANA by reacting with cytidine triphosphate (CTP). CMP-NANA synthetase catalyzes the reaction. CMP-NANA is the only nucleotide sugar in human metabolism in which the carrier nucleotide is a monophosphate rather than a diphosphate.

Acidic sugar synthesis

D-Glucuronic acid, whose structure is that of glucose with an oxidized carbon 6 ($-CH_2OH \rightarrow -COOH$), and its C-5 epimer, L-iduronic acid, are essential components of GAGs. Glucuronic acid is also required for the detoxification of lipophilic compounds, such as bilirubin, steroids, and many drugs, including the statins, because conjugation with glucuronate (glucuronidation) increases water solubility. In plants and mammals (other than guinea pigs and primates, including humans), glucuronic acid is a precursor of ascorbic acid (vitamin C) as shown in Figure 14.9. This uronic acid pathway also provides a mechanism by which dietary D-xylulose can enter the central metabolic pathways.

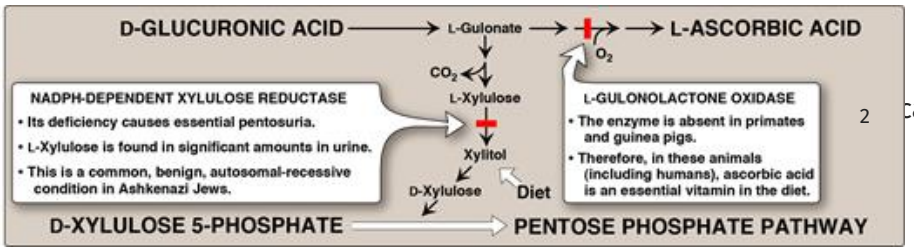
Glucuronic acid

Glucuronic acid can be obtained in small amounts from the diet and from the lysosomal degradation of GAGs. It also can be synthesized by the uronic acid pathway, in which glucose 1-phosphate reacts with uridine triphosphate (UTP) and is converted to UDP-glucose. Oxidation of UDP-glucose produces UDP-glucuronic acid, the form that supplies glucuronic acid for GAGs synthesis and glucuronidation (Fig. 14.10). The end product of glucuronic acid metabolism in humans is D-xylulose 5-phosphate, which can enter the pentose phosphate pathway and produce the glycolytic intermediates glyceraldehyde 3-phosphate and fructose 6-phosphate (see Fig. 14.9; see also Fig. 13.2).

L-Iduronic acid

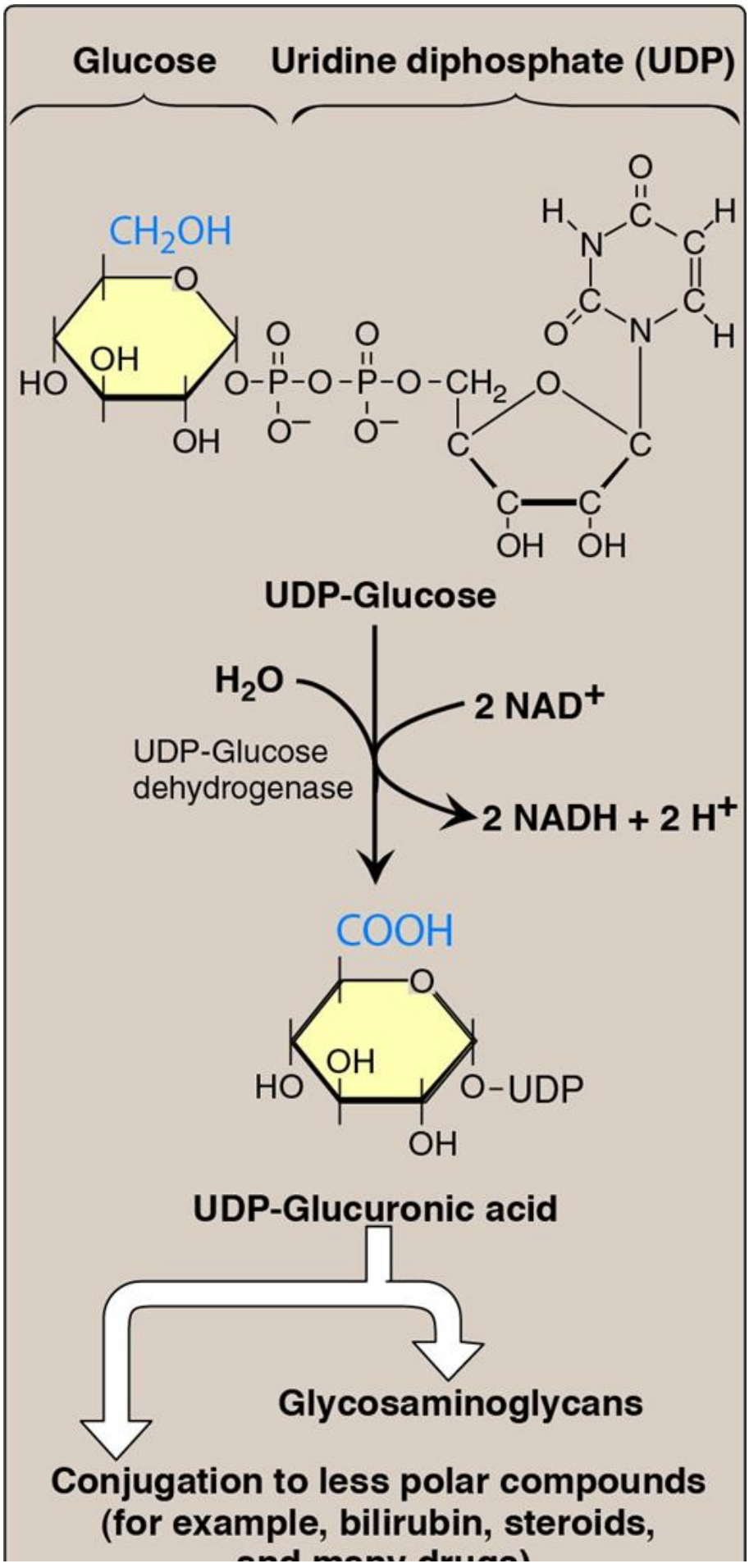
Synthesis of L-iduronic acid occurs after D-glucuronic acid has been incorporated into the carbohydrate chain. Uronosyl 5-epimerase causes epimerization of the D- to the L-sugar.

FIGURE 14.9



2 carbon dioxide.

FIGURE 14.10


Glucose
Uridine diphosphate (UDP)
UDP-Glucose
H2O
2 NAD+
UDP-Glucose dehydrogenase
2 NADH + 2 H+
UDP-Glucuronic acid
Glycosaminoglycans
Conjugation to less polar compounds
(for example, bilirubin, steroids,

and many drugs)

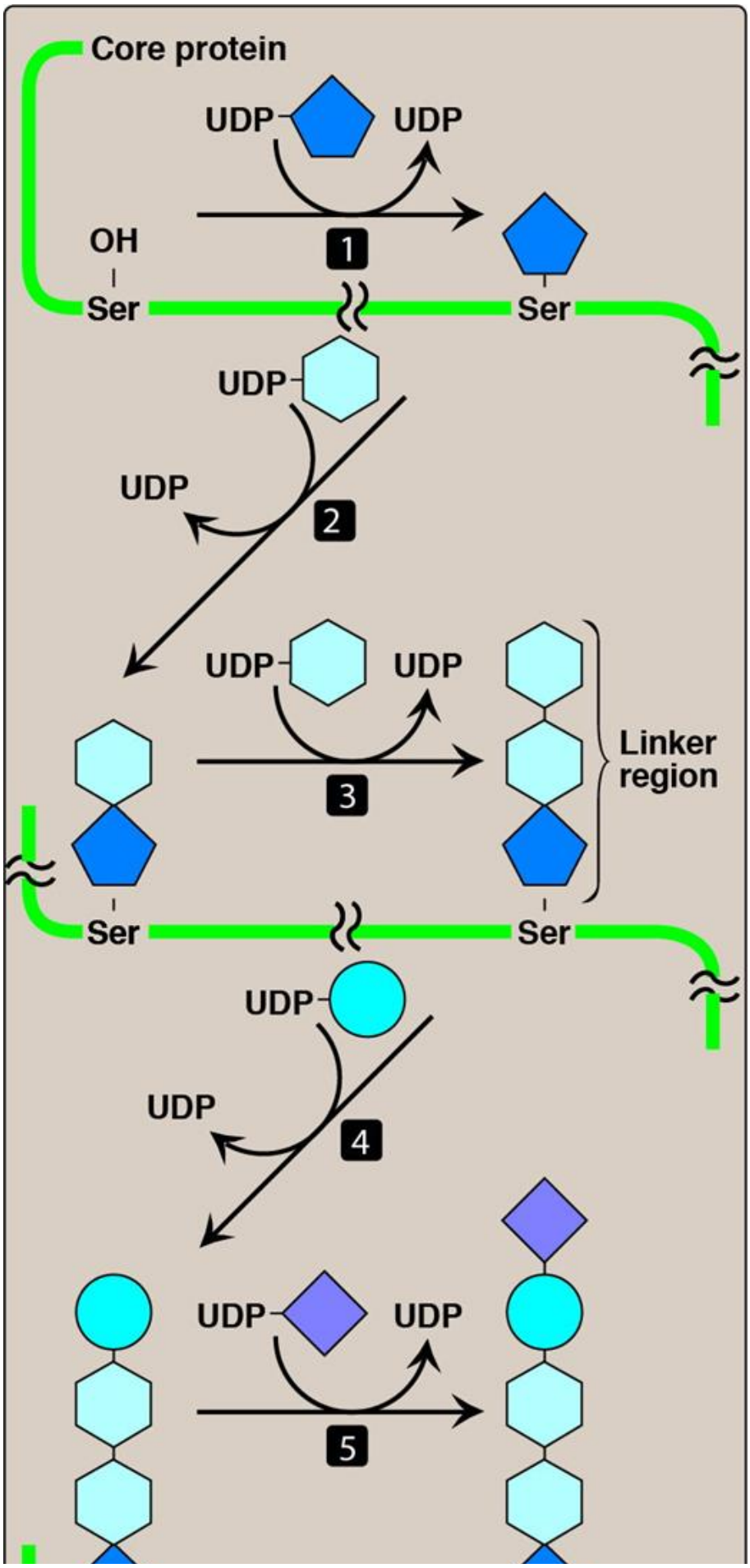
Core protein synthesis

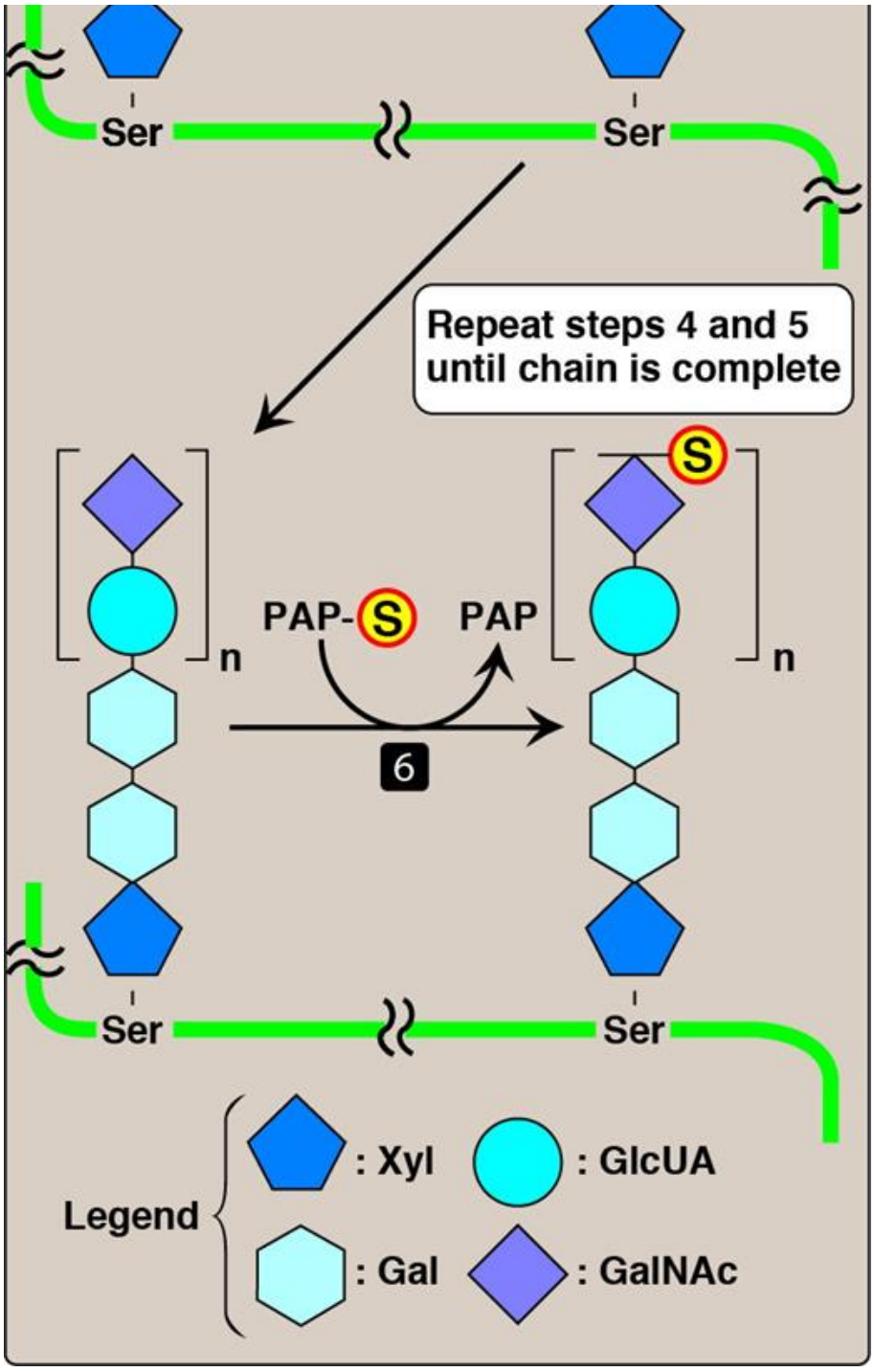
The core protein is made by ribosomes on the rough endoplasmic reticulum (RER), enters the RER lumen, and then moves to the Golgi, where it is glycosylated by membrane-bound glycosyltransferases.

Carbohydrate chain synthesis

Carbohydrate chain formation is initiated by synthesis of a short linker on the core protein on which carbohydrate chain synthesis will occur. The most common linker is a trihexoside formed by the transfer of a xylose from UDP-xylose to the hydroxyl group of a serine (or threonine) catalyzed by xylosyltransferase. Two galactose molecules are then added, completing the trihexoside. This is followed by sequential addition of alternating acidic and amino sugars (Fig. 14.11) and epimerization of some D-glucuronyl to L-iduronyl residues.

FIGURE 14.11


Core protein
UDP
UDP
OH
Ser
1
Ser
UDP
UDP
2
UDP
UDP
3
Linker region
Ser
Ser
UDP
UDP
4
UDP
UDP
5



Sulfate group addition

Sulfation of a GAG occurs after the monosaccharide to be sulfated has been incorporated into the growing carbohydrate chain. The source of the sulfate is 3′-phosphoadenosyl-5′-phosphosulfate (PAPS) a molecule of adenosine monophosphate with a sulfate group attached to the 5′-phosphate; see also Fig. 17.16. The sulfation reaction is catalyzed by sulfotransferases. Synthesis of the sulfated GAG chondroitin sulfate is shown in Figure 14.11. Note that PAPS is also the sulfur donor in glycosphingolipid synthesis.

Degradation

Listen

GAGs are degraded in lysosomes, which contain hydrolytic enzymes that are most active at a pH of ~5. Therefore, as a group, these enzymes are called acid hydrolases. The low pH optimum within lysosomes is a protective mechanism that prevents the enzymes from destroying the cell should leakage occur into the cytosol where the pH is neutral. [b]The half-lives of GAGs vary from minutes to months and are influenced by the type of GAG and its location in the body.

[b]For more information on lysosomes, see *LIR Cell and Molecular Biology*, 2nd Ed. Chapter 5.

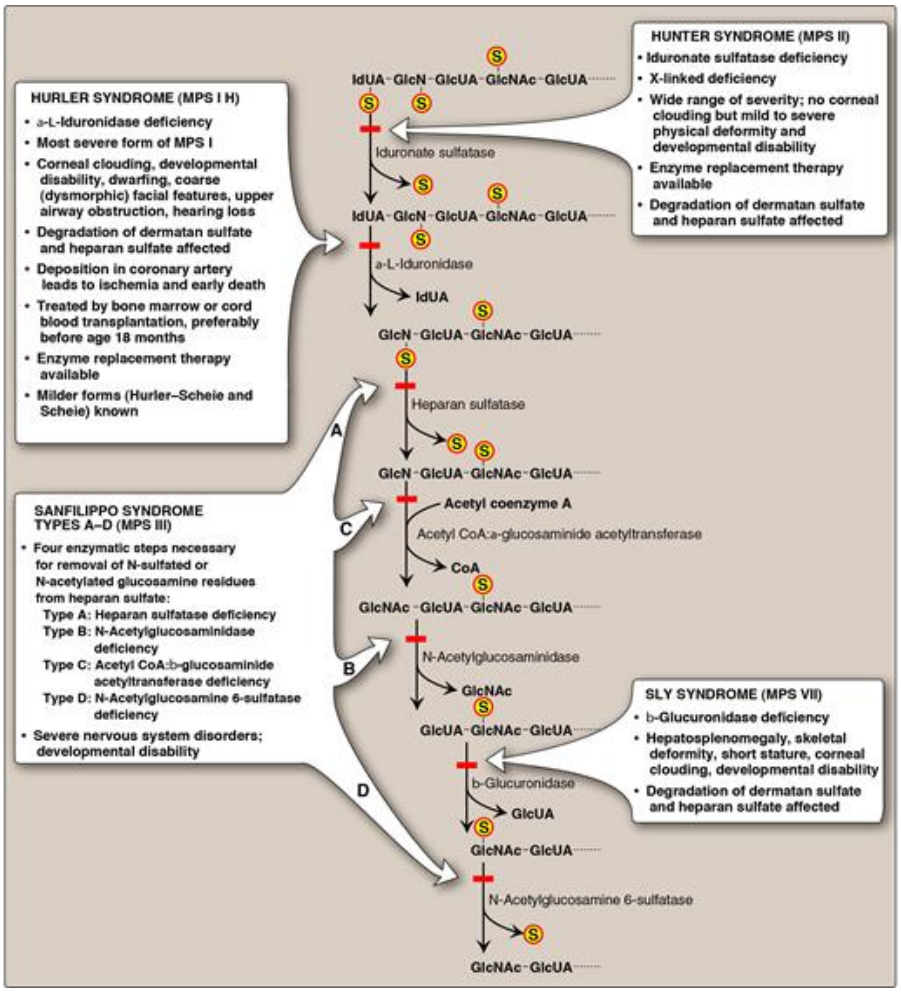
GAGs and phagocytosis

Because GAGs are extracellular or cell-surface compounds, they must first be engulfed by invagination of the cell membrane (phagocytosis), forming a vesicle inside of which are the GAGs to be degraded. This vesicle then fuses with a lysosome, forming a single digestive vesicle in which the GAGs are efficiently degraded.

Lysosomal degradation

The lysosomal degradation of GAGs requires a large number of acid hydrolases for complete digestion. First, the polysaccharide chains are cleaved by endoglycosidases, producing oligosaccharides. Further degradation of the oligosaccharides occurs sequentially from the nonreducing end of each chain, the last group (sulfate or sugar) added during synthesis being the first group removed, by action of sulfatases or exoglycosidases. Examples of some of these enzymes and the bonds they hydrolyze are shown in Figure 14.12. (Note that endo- and exoglycosidases are also involved in the lysosomal degradation of glycoproteins and glycolipids. Deficiencies in these enzymes result in the accumulation of partially degraded carbohydrates, causing tissue damage.)

FIGURE 14.12



ɔmal enzymes, indicating sites of

oses (MPS).

at degrade keratan sulfate result in *ulfatase B* that degrades dermatan glucuronic and iduronic acids; GalNAc = ine; S = sulfate.

Multiple sulfatase deficiency (Austin disease) is a rare lysosomal storage disease in which all sulfatases are nonfunctional because of a defect in the formation of formylglycine, an amino acid derivative required at the active site for enzymatic activity to occur.

Mucopolysaccharidoses

Listen

Mucopolysaccharidoses are hereditary diseases (approximately 1:25,000 live births) caused by a deficiency of any one of the lysosomal hydrolases normally involved in the degradation of heparan sulfate, dermatan sulfate, and/or keratin sulfate (summarized in Fig. 14.12). They are progressive disorders characterized by lysosomal accumulation of GAGs in various tissues, causing a range of symptoms, such as skeletal and ECM deformities, and intellectual disability. All are autosomal-recessive disorders except Hunter syndrome, which has X-linked inheritance.

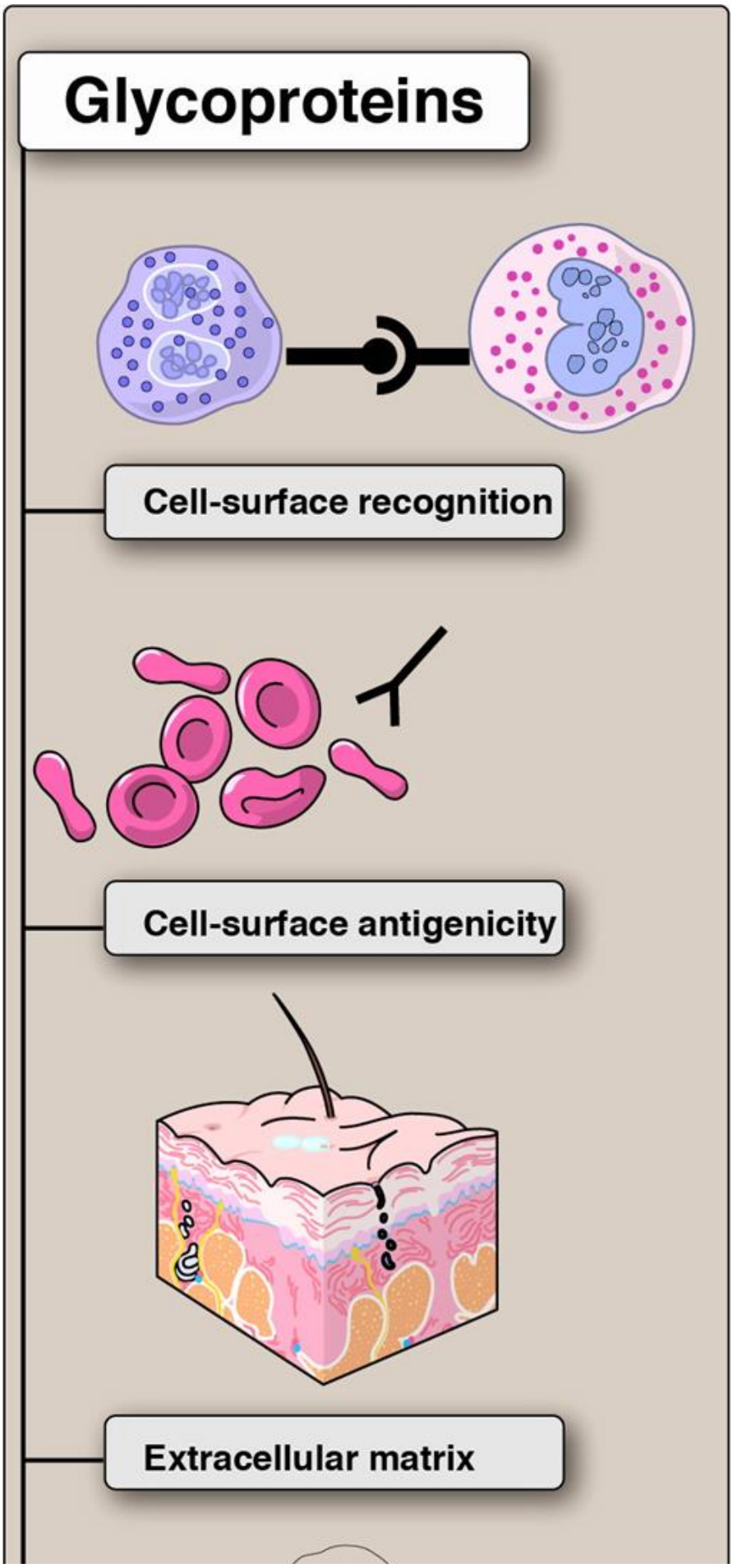
Children homozygous for any one of these diseases are apparently normal at birth and then gradually deteriorate. In severe deficiencies, death occurs in childhood. There currently is no cure. Incomplete lysosomal degradation of GAGs results in the presence of oligosaccharides in the urine. These fragments can be used to diagnose the specific mucopolysaccharidosis by identifying the structure present on the nonreducing end of the oligosaccharide, because that residue would have been the substrate for the missing enzyme. Diagnosis is confirmed by measuring the patient's cellular level of the lysosomal hydrolases. Bone marrow and cord blood transplants, in which transplanted macrophages produce the enzymes that degrade GAGs, have been used to treat Hurler and Hunter syndromes, with limited success. Enzyme replacement therapy is available for both syndromes but does not prevent neurologic damage.

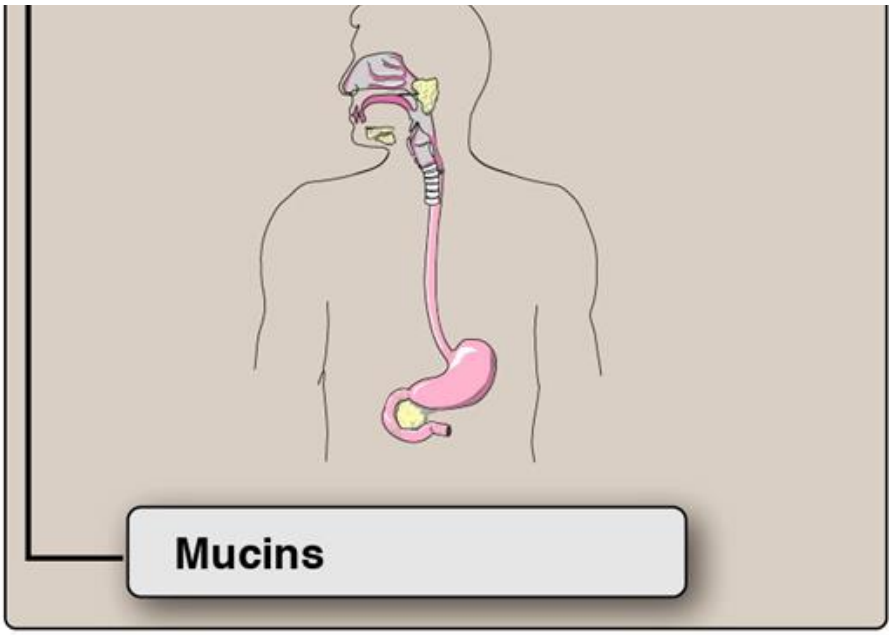
Glycoprotein Overview

Listen

Glycoproteins are proteins to which oligosaccharides (glycans) are covalently attached; *glycosylation* is the most common posttranslational modification of proteins. (Note: Nonenzymatic addition of carbohydrate to proteins is known as glycation.) Glycoproteins contain highly variable amounts of carbohydrate but typically much less than that of proteoglycans. For example, the glycoprotein immunoglobulin G (IgG) contains <4% of its mass as carbohydrate, whereas the proteoglycan aggrecan contains >80%. In glycoproteins, the glycan is relatively short, usually 2 to 10 sugar residues in length, is often branched instead of linear; and may or may not be negatively charged. Membrane-bound glycoproteins participate in a broad range of cellular phenomena, including cell-surface recognition by other cells, hormones, and viruses, cell-surface antigenicity (such as the blood group antigens), and as components of the ECM and of the mucins of the gastrointestinal and urogenital tracts, where they act as protective biologic lubricants. In addition, almost all of the globular proteins present in human plasma are glycoproteins, although albumin is an exception. Figure 14.13 summarizes some glycoprotein functions.

FIGURE 14.13


Glycoproteins
Cell-surface recognition
Cell-surface antigenicity
Extracellular matrix



Oligosaccharide Structure

Listen

The oligosaccharide (glycan) components of glycoproteins are generally branched heteropolymers composed primarily of D-hexoses, with the addition in some cases of neuraminic acid (a nonose) and of L-fucose, a 6-deoxyhexose.

Carbohydrate–protein linkage

The glycan may be attached to the protein through an N- or an O-glycosidic link (see p. 95). In the former case, the sugar chain is attached to the amide group of an asparagine side chain and, in the latter case, to the hydroxyl group of either a serine or threonine side chain. In the case of collagen, there is an O-glycosidic linkage between galactose or glucose and the hydroxyl group of hydroxylysine.

N- and O-linked oligosaccharides

A glycoprotein may contain only one type of glycosidic linkage (N or O linked) or may have both types within the same molecule.

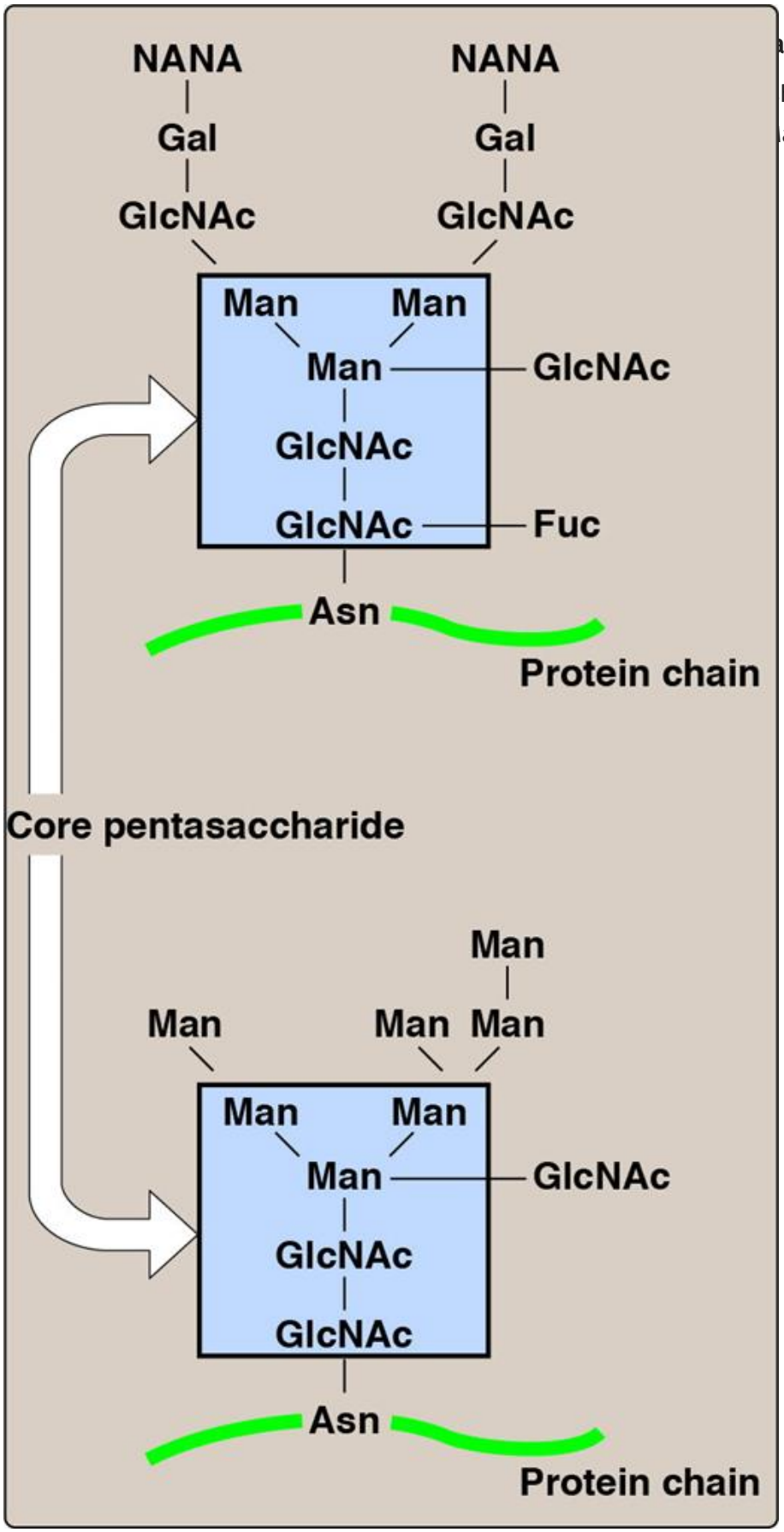
O linked

The O-linked glycans may have one or more of a wide variety of sugars arranged in either a linear or a branched pattern. Many are found in extracellular glycoproteins or as membrane glycoprotein components. For example, O-linked oligosaccharides on the surface of red blood cells help provide the ABO blood group determinants. If the terminal sugar on the glycan is GalNAc, the blood group is A. If it is galactose, the blood group is B. If neither GalNAc nor galactose is present, the blood group is O.

N linked

The N-linked glycans fall into two broad classes: complex oligosaccharides and high-mannose oligosaccharides. Both contain the same pentasaccharide core shown in Figure 14.14, but the complex oligosaccharides contain a diverse group of additional sugars, for example, GlcNAc, GalNAc, L-fucose, and NANA, whereas the high-mannose oligosaccharides contain primarily mannose.

FIGURE 14.14



arides.

hown inside the *box*].) NANA = N-

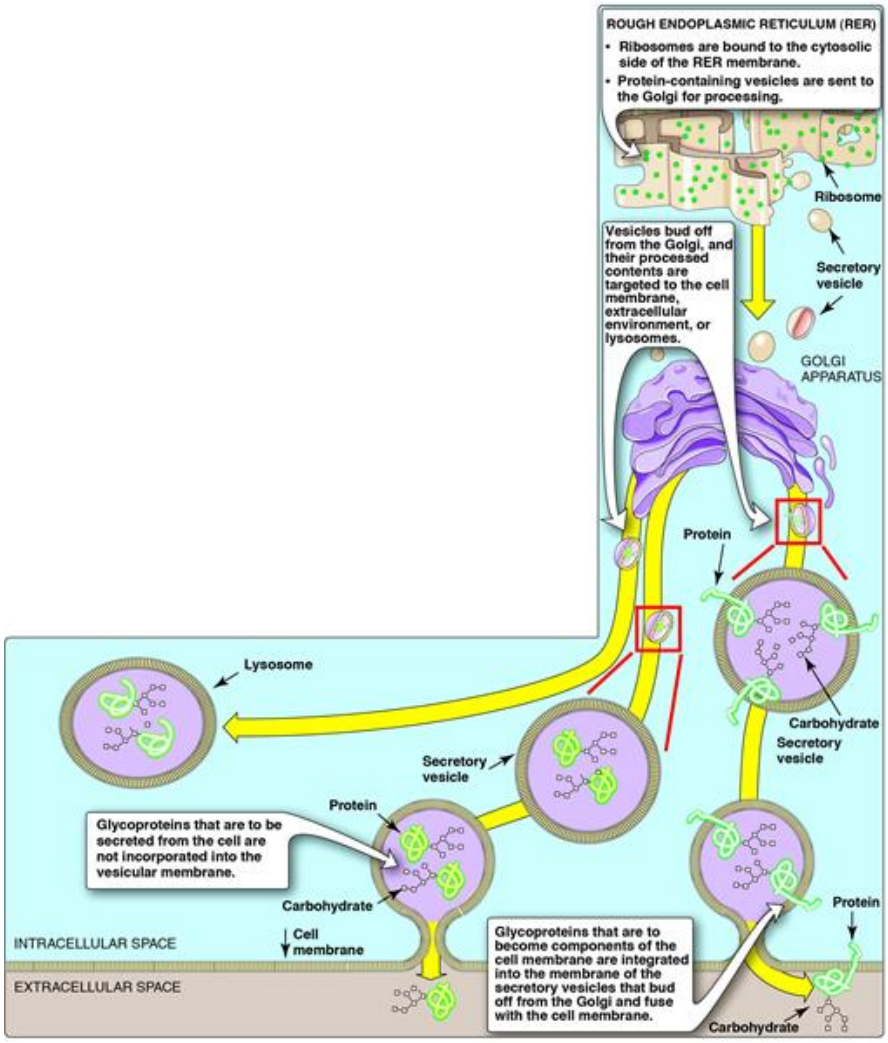
an = mannose; Fuc = fucose; Asn =

Glycoprotein Synthesis

Listen

Proteins destined to function in the cytoplasm are synthesized on free cytosolic ribosomes. However, proteins, including glycoproteins, that are destined for cellular membranes, lysosomes, or to be exported from the cell, are synthesized on ribosomes attached to the endoplasmic reticulum. These proteins contain specific signal sequences that act as molecular addresses, targeting the proteins to their proper destinations. An N-terminal hydrophobic sequence initially directs these proteins to the ER, allowing the growing polypeptide to be extruded into the lumen (see p. 505). The proteins are then transported via secretory vesicles to the Golgi, which acts as a sorting center (Fig. 14.15). In the Golgi, those glycoproteins that are to be secreted from the cell or targeted for lysosomes are packaged into vesicles that fuse with the plasma or lysosomal membrane and release their contents. Those that are destined to become components of the cell membrane are integrated into the Golgi membrane, which buds off, forming vesicles that add their membrane-bound glycoproteins to the cell membrane and are oriented with the carbohydrate portion facing toward the outside of the cell (see Fig. 14.15).

FIGURE 14.15



ıbsequent secretion or

Carbohydrate components

The precursors of the carbohydrate components of glycoproteins are nucleotide sugars, which include UDP-glucose, UDP-galactose, UDP-GlcNAc, and UDP-GalNAc. In addition, guanosine diphosphate (GDP)-mannose, GDP-L-fucose (synthesized from GDP-mannose), and CMP-NANA may donate sugars to the growing chain. When the acidic NANA is present, the oligosaccharide has a negative charge at physiologic pH. The oligosaccharides are covalently attached to the side chains of specific amino acids in the protein, where the three-dimensional structure of the protein determines whether or not a specific amino acid is glycosylated.

O-Linked glycoprotein synthesis

Synthesis of the O-linked glycoproteins is very similar to that of the GAGs. First, the protein to which sugars are to be attached is synthesized on the RER and extruded into its lumen. Glycosylation begins with the transfer of GalNAc (from UDP-GalNAc) to the hydroxyl group of a specific serine or threonine residues. The glycosyltransferases responsible for the stepwise synthesis (from individual sugars) of the oligosaccharides are bound to the membranes of the Golgi. They act in a specific order, without using a template as is required for DNA, ribonucleic acid (RNA), and protein synthesis (see Unit VII), but instead by recognizing the actual structure of the growing oligosaccharide as the appropriate substrate.

N-Linked glycoprotein synthesis

Synthesis of N-linked glycoproteins occurs in the lumen of the RER and requires the participation of the phosphorylated form of dolichol (dolichol pyrophosphate), a lipid of the RER membrane (Fig. 14.16). The initial product is processed in the RER and Golgi.

Dolichol-linked oligosaccharide synthesis

As with the O-linked glycoproteins, the protein is synthesized on the RER and enters its lumen. However, it does not become glycosylated with individual sugars. Instead, a lipid-linked oligosaccharide is first constructed. This consists of dolichol, an RER membrane lipid made from an intermediate of cholesterol synthesis (see p. 245) attached through a pyrophosphate linkage to an oligosaccharide containing GlcNAc, mannose, and glucose. The sugars to be added sequentially to the dolichol by membrane-bound glycosyltransferases are first GlcNAc, followed by mannose and glucose (see Fig. 14.16). The entire 14-sugar oligosaccharide is then transferred from dolichol to the amide nitrogen of an asparagine residue in the protein to be glycosylated by a *protein–oligosaccharide transferase* present in the RER. (Note: The antibiotic Tunicamycin inhibits N-linked glycosylation.)

Congenital disorders of glycosylation (CDG) are syndromes caused primarily by defects in the N-linked glycosylation of proteins, either oligosaccharide assembly (type I) or processing (type II).

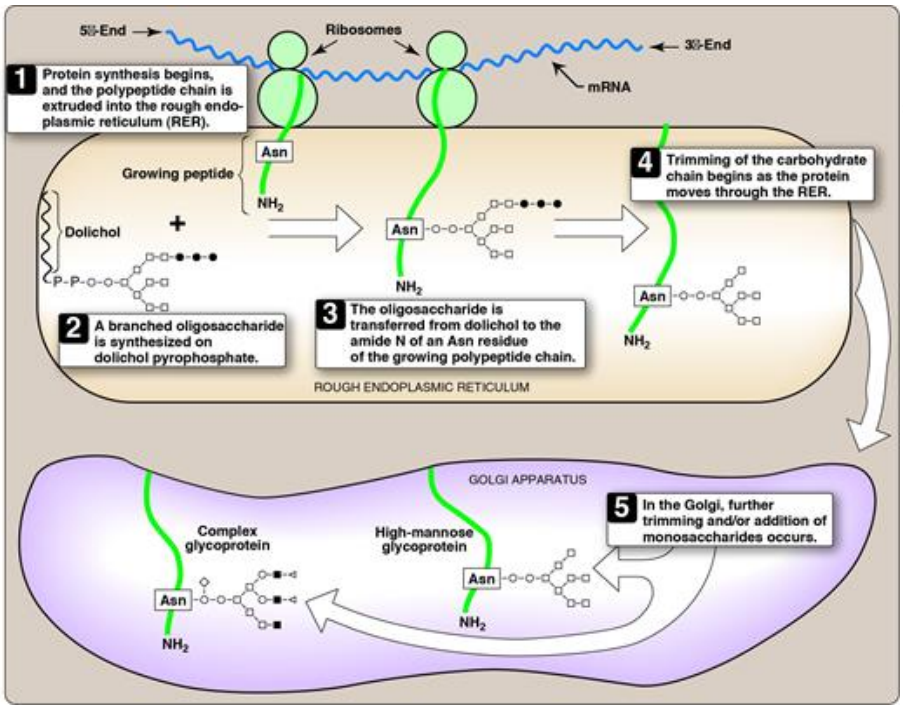
N-Linked oligosaccharide processing

After addition to the protein, the N-linked oligosaccharide is processed by the removal of specific mannosyl and glucosyl residues as the glycoprotein moves through the RER. Finally, the oligosaccharide chains are completed in the Golgi by addition of a variety of sugars (e.g., GlcNAc, GalNAc, and additional mannoses and then fucose or NANA as terminal groups) to produce a complex glycoprotein. Alternatively, they are not processed further, leaving branched, mannose-containing chains in a high-mannose glycoprotein (see Fig. 14.16). The ultimate fate of N-linked glycoproteins is the same as that of the O-linked glycoproteins (e.g., they can be released by the cell or become part of a cell membrane). In addition, N-linked glycoproteins can be targeted to the lysosomes.

Lysosomal enzymes

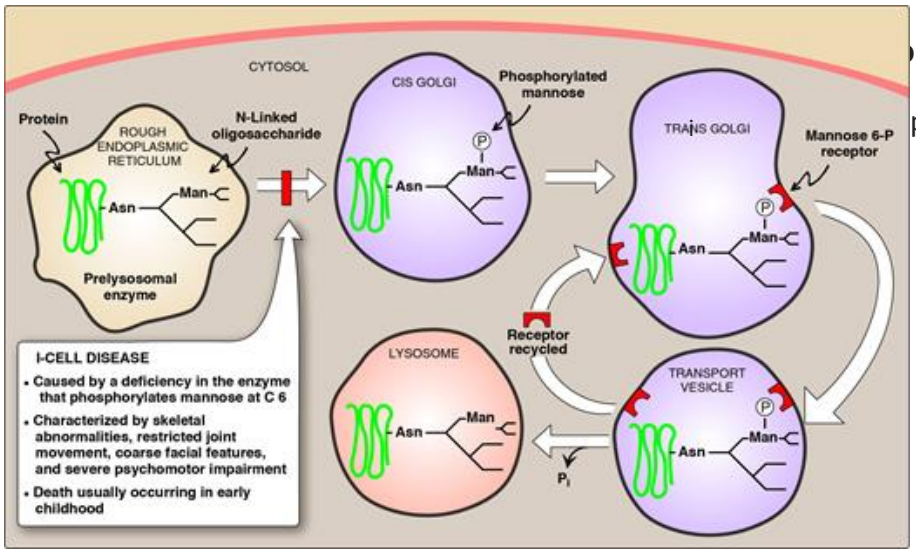
N-Linked glycoproteins being processed in the Golgi can be phosphorylated on carbon 6 of one or more mannosyl residues. UDP-GlcNAc provides the phosphate in a reaction catalyzed by a phosphotransferase. Receptors, located in the Golgi membrane, bind the mannose 6-phosphate (M6P) residues of these proteins, which are then packaged into vesicles and sent to the lysosomes (Fig. 14.17).

FIGURE 14.16



= terminal group (fucose or N-

FIGURE 14.17



…omes.

…phate.

CLINICAL APPLICATION 14.2

I-Cell Disease

I-Cell disease is a rare lysosomal storage disease named for large inclusion bodies seen in cells of patients with the disease. GlcNAc phosphotransferase is deficient and mannose 6-phosophate is not generated on proteins destined for lysosomes. Lack of M6P on amino acid residues causes precursor acid hydrolases to traffic to the plasma membrane and be secreted constitutively, instead of trafficking to lysosomes. Consequently, the acid hydrolases are absent from lysosomes, and the macromolecule substrates for these digestive enzymes accumulate within the lysosomes, generating the inclusion bodies that define the disorder. In addition, high concentrations of lysosomal enzymes are found in the patient's plasma and urine, indicating that the targeting process to lysosomes is deficient.

I-Cell disease is characterized by skeletal abnormalities, restricted joint movement, coarse (dysmorphic) facial features, and severe psychomotor impairment. Because I-cell disease has features in common with the mucopolysaccharidoses and sphingolipidoses, it is termed a mucolipidosis (ML II). Currently, there is no cure, and death from cardiopulmonary complications usually occurs in early childhood. Pseudo-Hurler polydystrophy (ML III) is a less severe mucolipidosis form of I-cell disease, in which the phosphotransferase maintains some residual enzymatic activity, and it symptomatically resembles a mild form of Hurler syndrome.

Lysosomal Glycoprotein Degradation

Listen

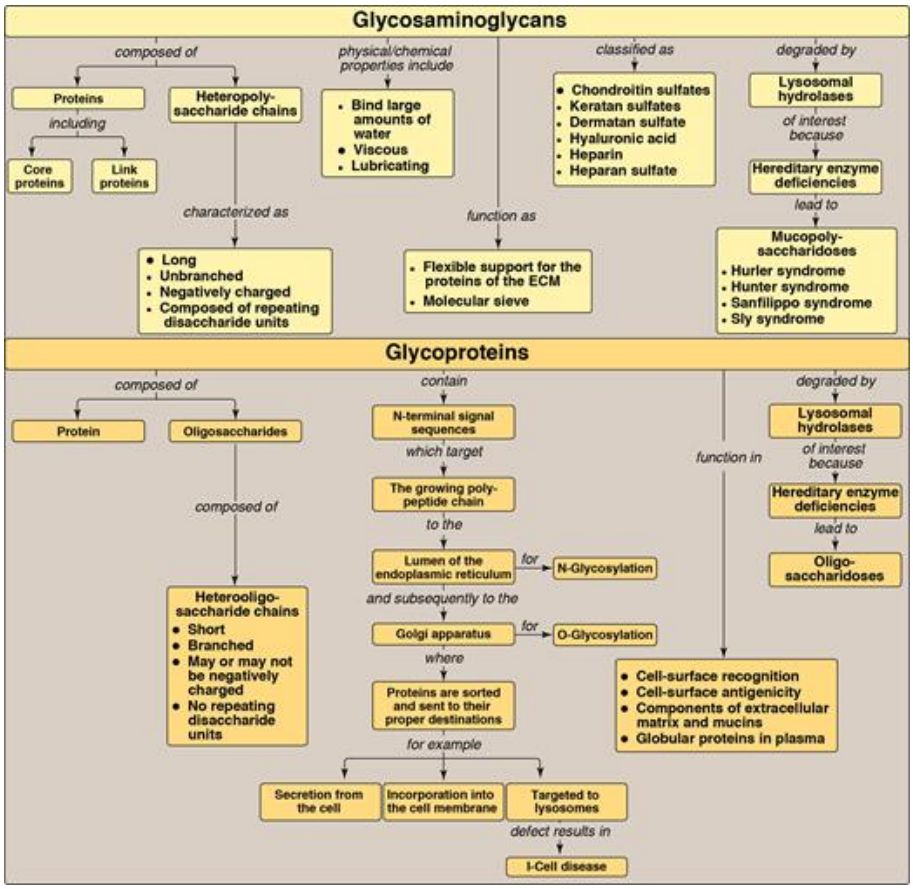
Degradation of glycoproteins is similar to that of the GAGs (see p. 179). The lysosomal acid hydrolases are each generally specific for the removal of one component of the glycoprotein. They are primarily exoenzymes that remove their respective groups in the reverse order of their incorporation (last on, first off). If any of the degradative enzyme is missing, degradation by the other exoenzymes cannot continue.

A group of very rare autosomal-recessive diseases called the glycoprotein storage diseases (oligosaccharidoses), caused by a deficiency of any one of the degradative enzymes, results in accumulation of partially degraded structures in the lysosomes. For example, α-mannosidosis type 3 is a severe, progressive, fatal deficiency of the enzyme α-mannosidase. Presentation is similar to Hurler syndrome, but immune deficiency is also seen. Mannose-rich oligosaccharide fragments appear in the urine. Diagnosis is by enzyme activity assay.

Chapter Summary

- **GAGs** are synthesized in the Golgi as **long**, **negatively charged**, **unbranched**, **heteropolysaccharide chains** generally composed of a **repeating disaccharide unit** (acidic sugar–amino sugar)$_n$.

FIGURE 14.18



- The **amino sugar** is either **d-glucosamine** or **d-galactosamine** and the **acidic sugar** is either **d-glucuronic acid** or its C-5 epimer **l-iduronic acid**.
- GAGs bind water, thereby producing the gel-like matrix that forms the basis of the body's **ground substance** and the lubricating properties of mucous secretions.
- There are six major types of GAGs: **chondroitin 4-** and **6-sulfates**, **keratan sulfate**, **dermatan sulfate**, **heparin**, **heparan sulfate**, and **hyaluronic acid**.
- All GAGs, except hyaluronic acid, are found covalently attached to a **core protein**, forming **proteoglycan monomers**. Many proteoglycan monomers associate with a molecule of **hyaluronic acid** to form **proteoglycan aggregates**.
- The completed proteoglycans are secreted into the **ECM** or remain associated with the outer surface of cells.
- GAGs are degraded by **lysosomal acid hydrolases**. A deficiency of any one of the hydrolases results in a **mucopolysaccharidosis** in which GAGs accumulate in tissues, causing symptoms such as **skeletal** and **ECM deformities** and **intellectual disability**. Examples of these genetic diseases include **Hunter** (X-linked) and **Hurler syndromes**.
- **Glycoproteins** are synthesized in the RER and Golgi and are proteins to which **oligosaccharides** (**glycans**) are covalently attached.

- **Membrane-bound** glycoproteins participate in **cell-surface recognition**, **cell-surface antigenicity**, and as components of the ECM 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.
- Precursors of carbohydrate components of glycoproteins are **nucleotide sugars**. **O-Linked glycoproteins** are produced in the Golgi by the sequential transfer of sugars from their nucleotide carriers to the hydroxyl group of a Ser or Thr residue in the protein. **N-Linked glycoproteins** are created by the transfer of a preformed oligosaccharide from its RER membrane lipid carrier, **dolichol pyrophosphate**, to the amide N of an Asn residue in the protein. They contain varying amounts of **mannose**.
- A deficiency in **N-acetylglucosamine phosphotransferase** that phosphorylates mannose residues at carbon 6 in N-linked glycoprotein enzymes destined for the lysosomes results in **I-cell disease**.
- Glycoproteins are normally degraded in lysosomes by **acid hydrolases**. A deficiency of any one of these enzymes results in a **lysosomal glycoprotein storage disease**, resulting in accumulation of partially degraded glycoproteins in the lysosome and causing a range of symptoms including skeletal deformity and intellectual disability.

Study Questions

Choose the ONE best answer.

14.1. Mucopolysaccharidoses are hereditary lysosomal storage diseases caused by:

A. defects in the degradation of glycosaminoglycans.

B. abnormal targeting of acid hydrolase 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.

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.

14.2. The presence of the following compound in the urine of a patient suggests a deficiency in which one of the enzymes listed below?

A. Galactosidase

B. Glucuronidase

C. Iduronidase

D. Mannosidase

E. Sulfatase

Correct answer = E. Degradation of glycoproteins follows the rule: last on, first off. Because sulfation is the last step in the synthesis of this sequence, a sulfatase is required for the next step in the degradation of the compound shown.

14.3. An 8-month-old male has coarse facial features, skeletal abnormalities, and delays in both growth and development. I-cell disease is suspected. Which of the following will be observed in this patient if that diagnosis is correct?

A. Decreased production of cell surface O-linked glycoproteins.

B. Elevated levels of acid hydrolases in the blood.

C. Inability to N-glycosylate proteins.

D. Increased synthesis of proteoglycans.

E. Oligosaccharides in the urine.

Correct answer = B. I-Cell disease is a lysosomal storage disease caused by deficiency of the phosphotransferase needed for synthesis of the mannose 6-phosphate signal that targets acid hydrolases to the lysosomal matrix. This results in secretion of these enzymes from the cell and accumulation of materials within the lysosome because of impaired degradation. None of the other choices relates to I-cell disease or lysosomal function. Oligosaccharides in the urine are characteristic of the muco- and polysaccharidoses but not I-cell disease (a type II mucolipidosis).

14.4. An infant with corneal clouding has dermatan sulfate and heparan sulfate in his urine. Decreased activity of which of the enzymes listed below would confirm the suspected diagnosis of Hurler syndrome?

A. α-L-Iduronidase

B. α-Glucuronidase

C. Glycosyltransferase

D. Iduronate sulfatase

Correct answer = A. Hurler syndrome, a defect in the lysosomal degradation of glycosaminoglycans (GAGs) with corneal clouding, is due to a deficiency in α-L-iduronidase. β-Glucuronidase is deficient in Sly syndrome, and iduronate sulfatase is deficient in Hunter syndrome. Glycosyltransferases are enzymes of GAGs synthesis.

14.5. A 67-year-old male presents for evaluation of pain and stiffness in his left knee and is diagnosed with osteoarthritis. Decreases in which of the following contribute to his symptoms?

A. Lysosomal acid hydrolases

B. Cartilage proteoglycans

C. Cell-surface O-linked glycoproteins

D. Golgi phosphotransferase

Correct answer = B. Proteoglycans contribute to the resilience of cartilage. In osteoarthritis, cartilage has degraded and the protection normally provided by proteoglycans is lost. The disease is not caused by lysosomal defects including trafficking or function of acid hydrolases.