Glycosaminoglycans: Anionic polysaccharide chains made of repeating disaccharide units

- **Glycosaminoglycans** present on the animal cell surface and in the extracellular matrix.
- Glycoseaminoglycans (mucopolysaccharides) are **linear** polymers of **repeating disaccharides** units containing a derivative of an amino sugar, either glucosamine or galactosamine
- The constituent monosaccharides tend to be **modified**, with acidic groups, amino groups, and sulfated hydroxyl etc.
- Glycosaminoglycans tend to be **negatively charged**, It is large complexes of negatively charged heteropolysaccharide Chains. This negative charge comes from the prevalence of acidic groups (carboxylate) or due to the presence of sulfate group.
- The Sulfate esters on some of the hydroxyl groups give these polymers a high density of negative charge, forcing them to assume extended conformations.

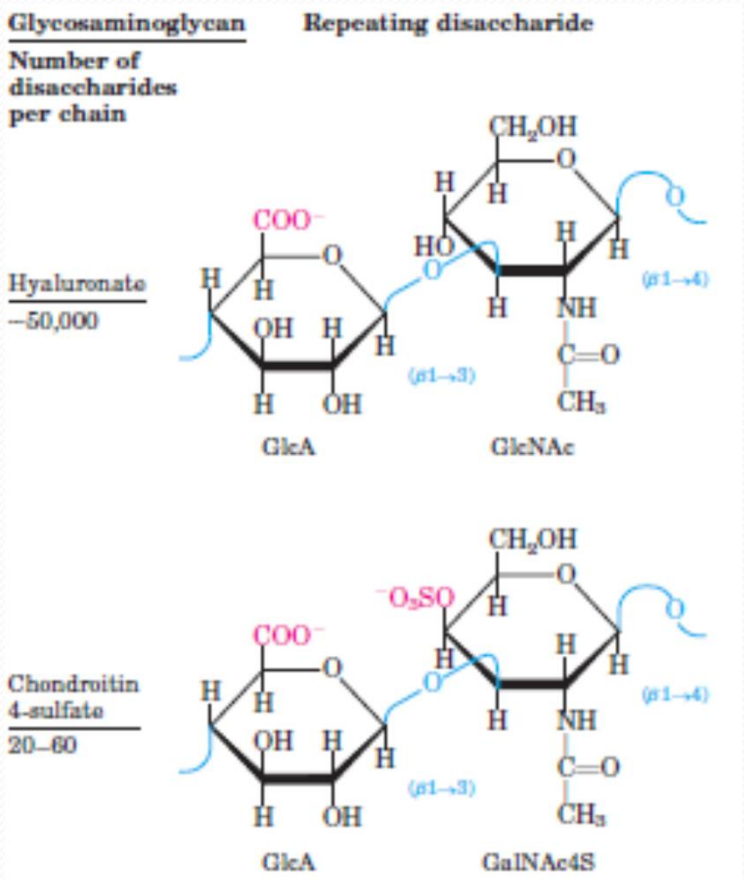
Glycosaminoglycans: (cont.)

- **So, glycoseaminoglycans have the following properties:**
- Can bind large amounts of water
- Gel-like matrix
- Viscous, Lubricating
- Shock absorbing
- Negatively charged

- Examples: Chondroitin sulfate, keratan sulfate, heparin, dermatan sulfate, and hyaluronate

- Glycosaminoglycans are usually attached with a small (<5%) amount of protein forming proteoglycans

Repeating units of some common glycos-aminoglycans of extracellular matrix



Examples of Glycosaminoglycans

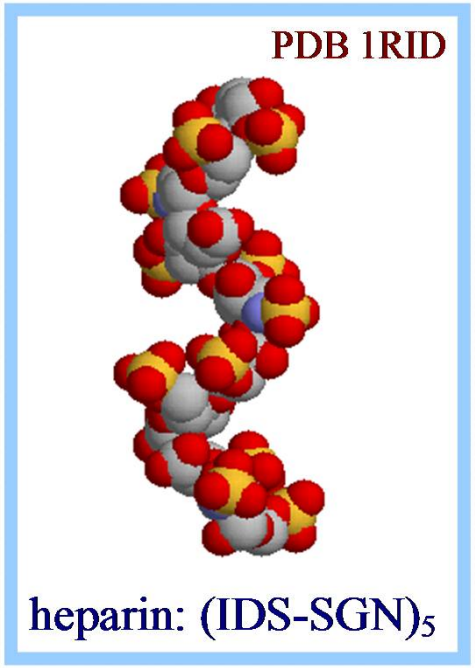
Heparin, is a soluble glycosaminoglycan act as natural anticoagulant and is synthesized in the mast cells in a nonsulfated form, which is then deacetylated and sulfated.

When released into the blood, it inhibits clot formation by interacting with the protein antithrombin.

It has a structure similar to that of heparan sulfates, but is more **highly sulfated**.

Heparin has an **extended helical conformation**.

Heparin shown has 10 residues, alternating IDS (iduronate-2-sulfate) & SGN (N-sulfo-glucosamine-6-sulfate).



Heparin has the highest negative charge density of any known biological macromolecule. The charge repulsion by the many negatively charged groups may contribute to its conformation.

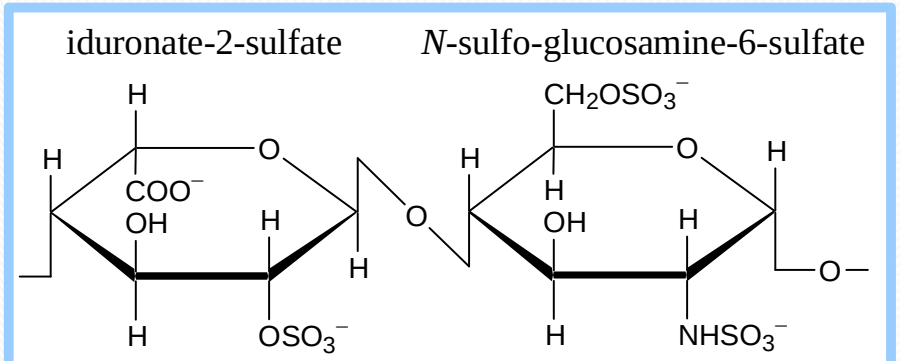
Purified heparin is routinely added to blood samples obtained for clinical analysis, and to blood donated for transfusion, to prevent clotting.

Examples of Glycosaminoglycans
Heparan sulfate

Heparan sulfate is initially synthesized on a membrane-embedded core protein as a polymer of alternating ***N*-acetylglucosamine** and **glucuronate** residues.

Heparan sulfate is like heparin except that it has :

- fewer N- and O-sulfate groups
- more acetyl groups.

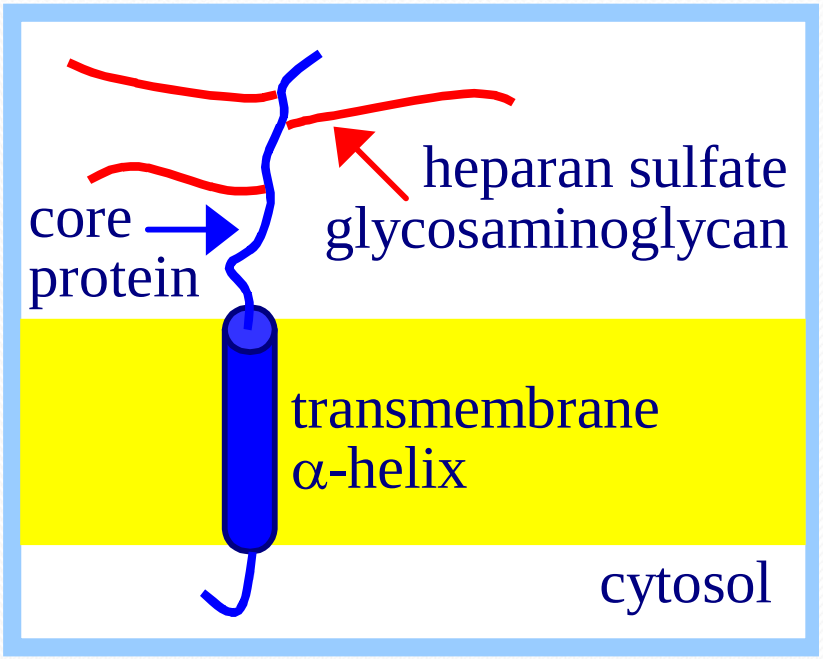


heparin or heparan sulfate - examples of residues

Later, in segments of the polymer, glucuronate residues may be converted to the sulfated sugar **iduronic acid**, while *N*-acetylglucosamine residues may be deacetylated and/or sulfated to give heparin.

Some **cell surface heparan sulfate** glycosaminoglycans remain covalently linked to core proteins embedded in the plasma membrane.

The core protein of a **syndecan** heparan sulfate proteoglycan includes a single **transmembrane α-helix.**



Syndecans are single transmembrane domain proteins that act as co-receptors. These core proteins carry three to five heparan sulfate and chondroitin sulfate chains, which allow for interaction with a large variety of ligands

The core protein of a **glypican** heparan sulfate proteoglycan is attached to the outer surface of the plasma membrane via **covalent linkage to** a modified phosphatidylinositol **lipid**.

Glypicans constitute one of the two major families of heparin sulfate proteoglycans. They seem to play a vital role in morphogenesis, and have been suggested as regulators for some cell signaling pathways.

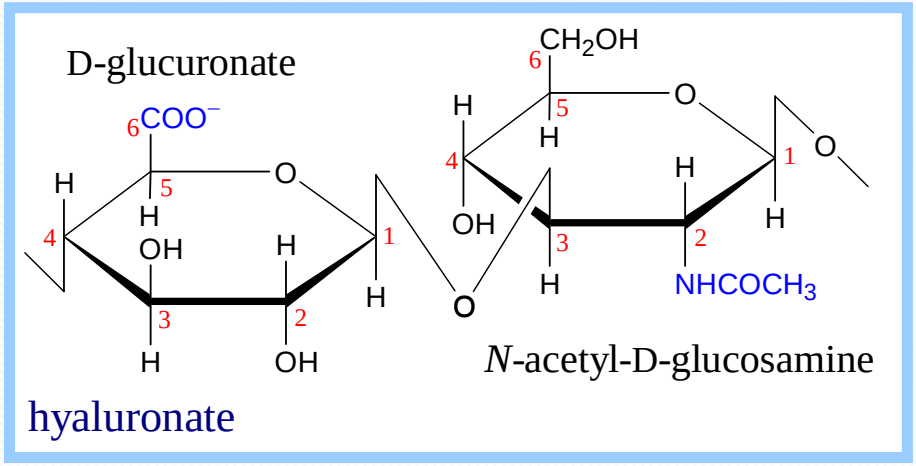
Proteins involved in **signaling** & **adhesion** at the cell surface recognize & bind heparan sulfate chains.

E.g., binding of some **growth factors** (small proteins) to cell surface receptors is enhanced by their binding also to heparan sulfates.

Regulated cell surface **Sulf** enzymes may **remove sulfate** groups at particular locations on heparan sulfate chains to **alter affinity** for signal proteins, e.g., growth factors.

Examples of Glycosaminoglycans
Hyaluronate

Hyaluronate *(hyaluronan)* is an α-glycosaminoglycan that is found in extracellular tissue space, the synovial fluid of joints, and the vitreous humor of the eyes and acts as a binding, lubricating, and protective agent.

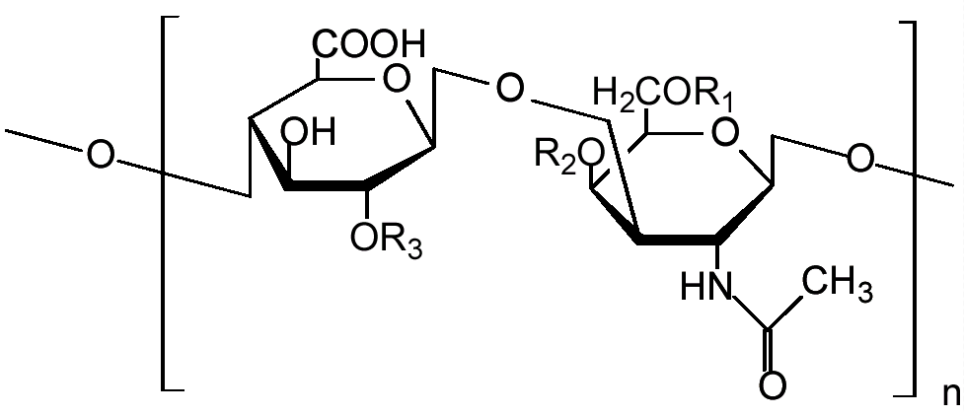


Hyaluronate is a repeating disaccharide consisting of 2 glucose derivatives, glucuronate (glucuronic acid) & *N*-acetyl-glucosamine.

The glycosidic linkages are β(1→3) & β(1→4).

Examples of Glycosaminoglycans

Chondroitin sulfate



- ***Chondroitin sulfate*** is unbranched polysaccharides.
- It is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars (N-acetylgalactosamine and glucuronic acid). Typically attached to proteins as part of a proteoglycan.
- It helps with tensile strength of cartilage, tendons, and ligaments.

Peptidoglycan

- Peptidoglycan, also known as **murein**, is a polymer consisting of sugars and amino acids that forms a mesh-like layer outside the plasma membrane of most bacteria, forming the cell wall.
- The sugar component consists of alternating residues of β-(1,4) linked *N*-acetylglucosamine and *N*-acetylmuramic acid.
- Attached to the *N*-acetylmuramic acid is a peptide chain of three to *five amino acids*.
- ***In case of Escherichia coli (a Gram-negative bacterium) the amino acids are:***
  - L-alanine, D-glutamic acid, *meso*-diaminopimelic acid, and D-alanine
- ***In case of Staphylococcus aureus (a gram-positive bacterium) the amino acids are:***
  - L-alanine, D-glutamine, L-lysine, and D-alanine with a 5-glycine
- The peptidoglycan layer is substantially thicker in gram-positive bacteria (20 to 80 nanometers) than in gram-negative bacteria (7 to 8 nanometers).

Proteoglycans

- **Proteoglycans** are **glycosaminoglycans** that are covalently linked to **serine** residues of specific **core proteins**. The glycosaminoglycan chain is synthesized by sequential addition of sugar residues to the core protein.
- It resembles polysaccharides more than proteins (heavily glycosylated proteins) in as much as the carbohydrate makes up as much as **95%** of the biomolecule by weight.
- Proteoglycans function as lubricants and structural components in connective tissue and mediate adhesion of cells to the extracellular matrix.

Some proteoglycans of the extracellular matrix **bind** non-covalently to **hyaluronate** via protein domains called **link modules**. e.g.:

- Multiple copies of the **aggrecan** proteoglycan associate with hyaluronate in cartilage to form large complexes.
- **Versican**, another proteoglycan, binds hyaluronate in the extracellular matrix of loose connective tissues.

Glycoproteins

- Glycoproteins contain less carbohydrate than proteoglycans (1-30%).
- **Glycoproteins** have one or several oligosaccharides of varying complexity joined covalently to a protein.
- They are found inside and outside the cells:
  - Inside cells they are found in specific organelles such as Golgi complexes, secretory granules, and lysosomes.
  - Outside the cell on the outer face of the plasma membrane, in the extracellular matrix, and in the blood.
- The oligosaccharide portions of glycoproteins are rich in information, forming highly specific sites for recognition and high-affinity binding by other proteins.
- Cell-surface molecules are contributed to:
- antigen determinants
- mediator of cell-cell interaction
- attachment sites for viruses

Functions of Glycoproteins

- Gylcoproteins have many biological functions:
  - 1- Immunological protection
  - 2- Cell-cell recognition
  - 3- Blood clotting
  - 4- Host-pathogen interaction

Linkage between sugar and protein part in glycoproteins

- Carbohydrates link through the *anomeric* carbon to:
  - The amide nitrogen in the side chain of *asparagine* (N-glycosidic bond) or
  - The hydroxyl oxygen of *serine or threonine* (O-glycosidic bond)

Lipo-oligo vs lipo-polysaccharides

- The term lipo-oligosaccharide ("LOS") is used to refer to a low-molecular-weight small number of sugar molecules bound to lipid core.
- Lipopolysaccharides (LPS) or lipoglycans are larger molecules consisting of a lipid and a polysaccharide.
- It is composed of outer core and inner core joined by a covalent bond and found in the outer membrane of Gram-negative bacteria.

Lipopolysaccharides

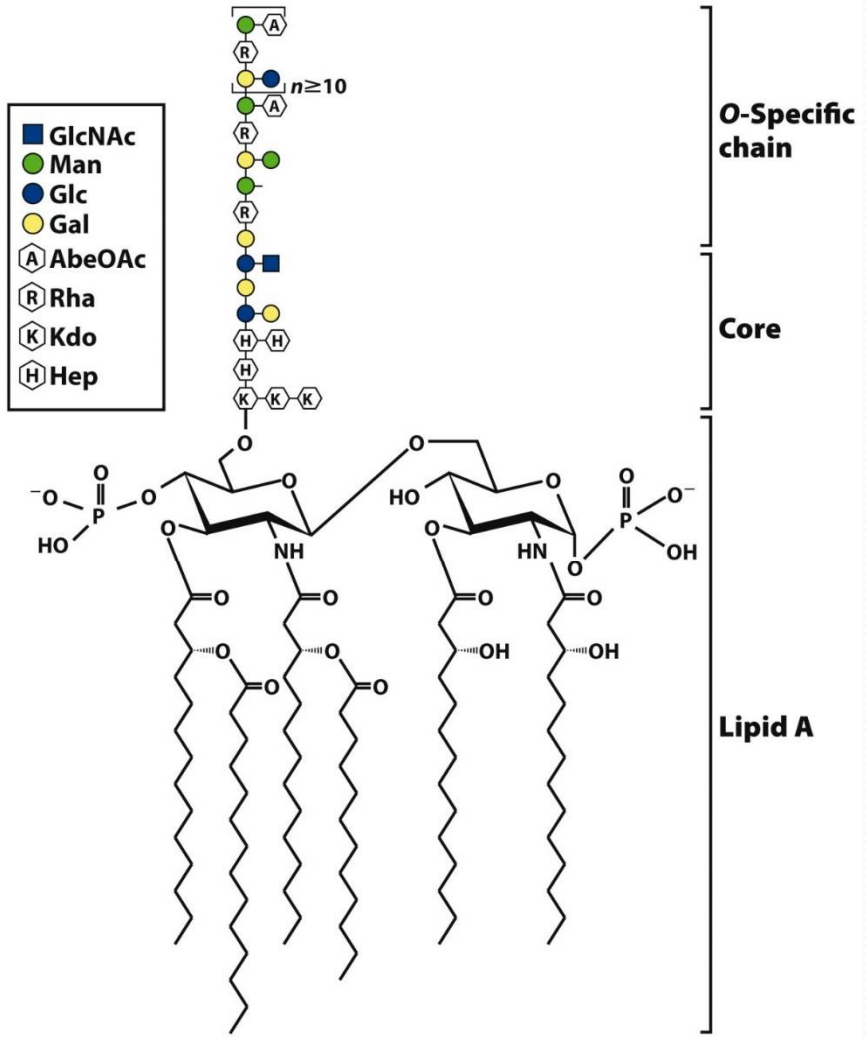


Figure 7-31
Lehninger Principles of Biochemistry, Sixth Edition

Lipopolysaccharide of the outer membrane of the bacterium *Salmonella typhimurium*

The addition of sugar moiety determines the blood group

- Sugars attached to glycoproteins and glycolipids on the surfaces of red blood cells determine the blood group termed A, B, and O.
- The A and B antigens differ from the O antigen by the addition of one extra monosaccharide through an α -1,3 linkage to a galactose moiety of the O antigen
    - *N*-acetylgalactosamine (for A)
    - galactose (for B).
- The addition of *N*-acetylgalactosamine or galactose is mediated by specific enzyme called glycosyltransferases which add the extra monosaccharide to the O antigen.
- Each person inherits the gene for one glycosyltransferase of this type from each parent.
    - The type A glycosyltransferases specifically adds *N*-acetylgalactosamine,
    - The type B glycosyltransferases adds galactose.
    - The O phenotype lack that enzyme due to mutation that leads to premature termination of translation and, hence, it produces inactive glycosyltransferase.