Mucopolysacharides (Glycosaminoglycans)

- Jeanloz has suggested the name Glycosaminoglycans (GAG) to describe this group of substances. They are usually composed of **amino sugar** and **uronic acid** units as the principal components, though some are chiefly made up of amino sugar and monosaccharide units without the presence of uronic acid. They are generally associated with a small amount of protein, forming (P**roteoglycans**), which typically consist of over 95% carbohydrate.
  - Glycosaminoglycans have the special ability to bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body's ground substance, which, along with fibrous structural proteins such as collagen and elastin, and adhesive proteins such as fibronectin, make up the extracellular matrix (ECM).
  - The hydrated glycosaminoglycans 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 glycosaminoglycans, which led to the original naming of these compounds as mucopolysaccharides.
  - Mucopolysaccharides are excreted in urine in abnormal amounts in the group of lysosomal storage disorders known as **mucopolysaccharidoses**. They can be detected by 2D gel electrophoresis techniques; some mucopolysaccharides can also be detected by simple urine screening tests like CPC test, Cetavlon test and Alcian blue staining.

  - Examples of mucopolysaccharides are hyaluronic acid, heparin,chondroitin sulfate, dermatan sulfate and keratan sulfate (see figures below).

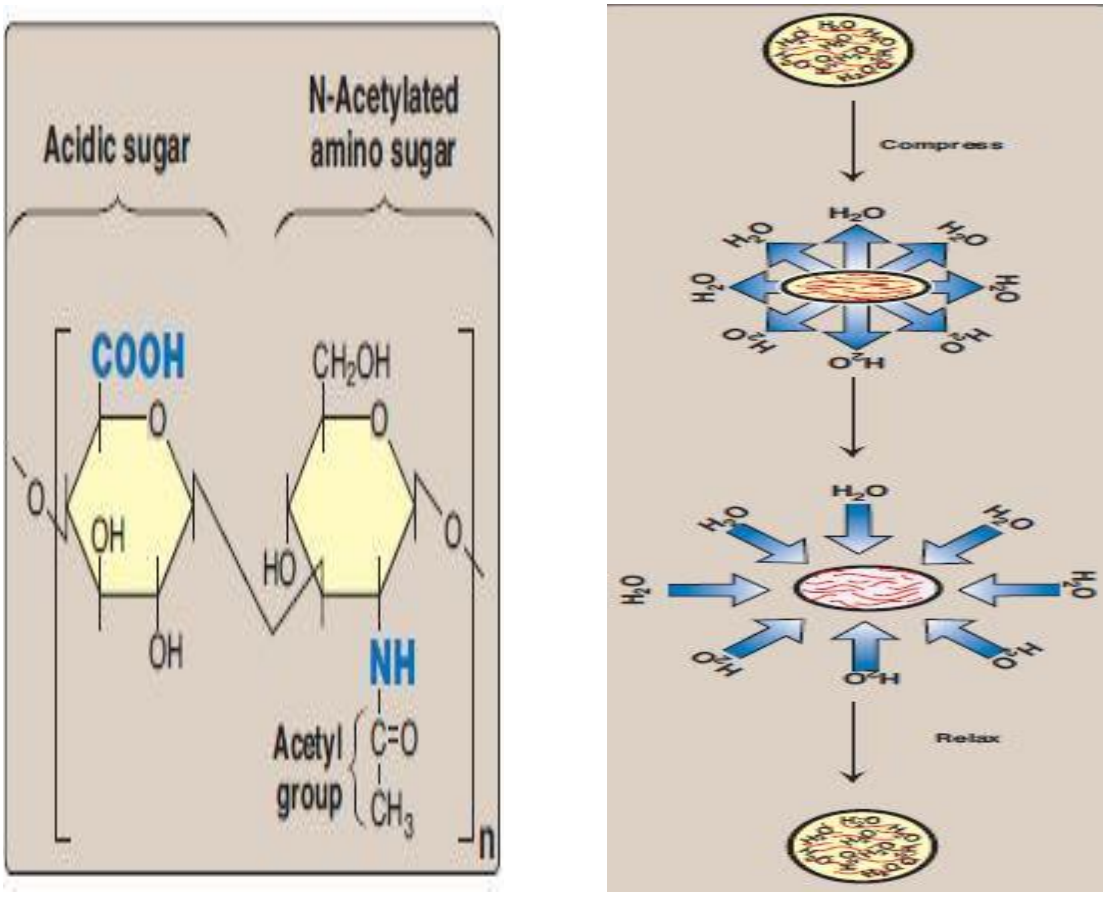


Figure 13: a-Repeating disaccharide unit (Mucopolysaccharides). b- Resilience of glycosaminoglycans.

Functions of Proteoglycans

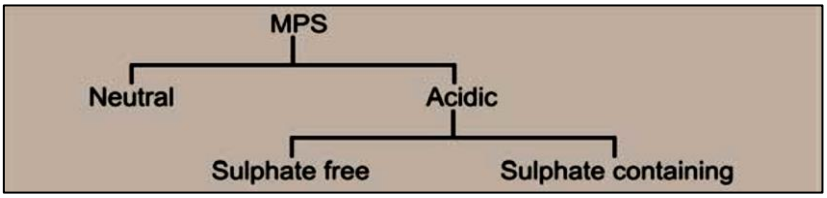
- **As a constituent of extracellular matrix or ground substance:** Interacts with collagen and elastin.
- **Acts as a barrier in tissue:** Hyaluronic acid in tissues acts as a cementing substance and contributes to tissue barrier which permit metabolites to pass through but **resist penetration by bacteria and other infective agents.**
- **Acts as Lbricant in joints:** Hyaluronic acid in joints acts as a lubricant and shock absorbent.
- **Role in release of hormone.**
- **Role in cell migration in embryonic tissues:** Hyaluronic acid is present in high concentration in embryonic tissues and is considered to play an important role in cell migration during morphogenesis and wound repair.
- **Role in sclera of eye:** Dermatan sulphate is present in sclera of the eye where it has an important function in maintaining overall shape of the eye.

- **Role in corneal transparency:** Keratan sulphate I is present in cornea of the eye and lie between the collagen fibrils. It plays an important role in maintaining corneal transparency.
- **Role in glomerular filtration.**
- **Acts as anticoagulant:**

  Heparin

- It is an anticoagulant widely used when taking blood in vitro for clinical studies.
- It is also used in vivo in suspected thromboembolic conditions to prevent intravascular coagulation. It activates antithrombin III, which in turn inactivates thrombin, factor X and factor IX.

List types of mucopolysacharides.



A- Sulphate free MPS:

1- Hyaluronic Acid
2- Chondroitin

B- Sulphate Containing Acid MPS:

1- Keratan Sulphate
2- Chondroitin Sulphates
3- Heparin
4- Heparitin Sulphate

C- Neutral

A-1- Hyaluronic Acid

A sulphate free mucopolysacharides. Later it was found to be present in synovial fluid, skin, umbilical cord.

Composition: It is composed of repeating units of ***N-acetyl glucosamine and D-Glucuronic acid.***

On hydrolysis, it yields equimolecular quantities of D-Glucosamine, D-Glucoronic acid and acetic acid (Fig. 14).

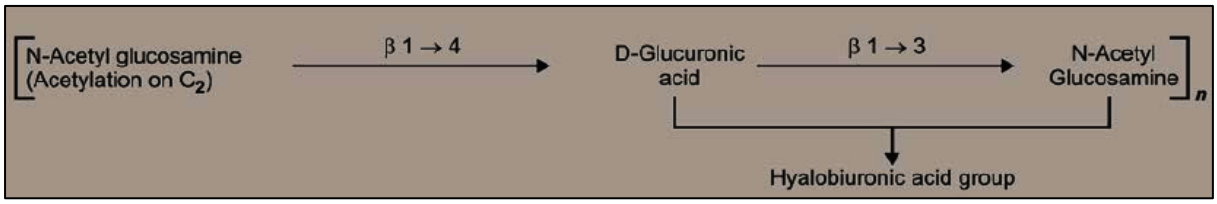


Figure 14: Structure of Hyaluronic acid

Biomedical Importance

The invasive power of some pathogenic organisms may be increased because they secrete **hyaluronidase.** In the testicular secretions, it may dissolve the viscid substances surrounding the ova to permit penetration of spermatozoa.

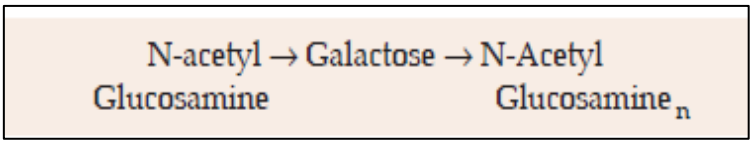
A-2- Chondroitin

Another sulphate free acid mucopolysaccharide. Found in cornea and has been isolated from cranial cartilages. It differs from hyaluronic acid only in that it contains N-acetyl galactosamine instead of N-acetyl glucosamine.

B-1- Keratan Sulphate (Kerato Sulphate)

A sulphate containing acid MPS. Found in costal cartilage, and cornea has been isolated from bovine cornea. It has been reported to be present in ***Nucleus pulposus*** and the wall of aorta.

Composition: It is composed of repeating disaccharide unit consisting of N-acetyl glucosamine and galactose (Figure 15).



B-2- Chondroitin Sulphates

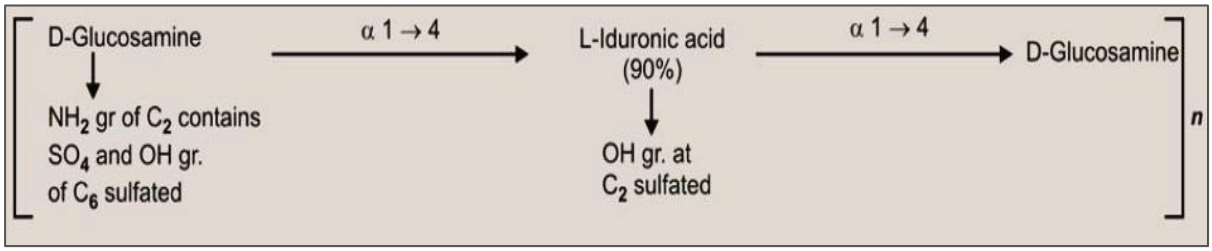
They are principal MPS in the ground substance of mammalian tissues and cartilage. They occur in combination with proteins and are called as Chondroproteins.

Four chondroitin sulphates have been isolated so far. They are named as chondroitin SO_4 A, B, C and D.

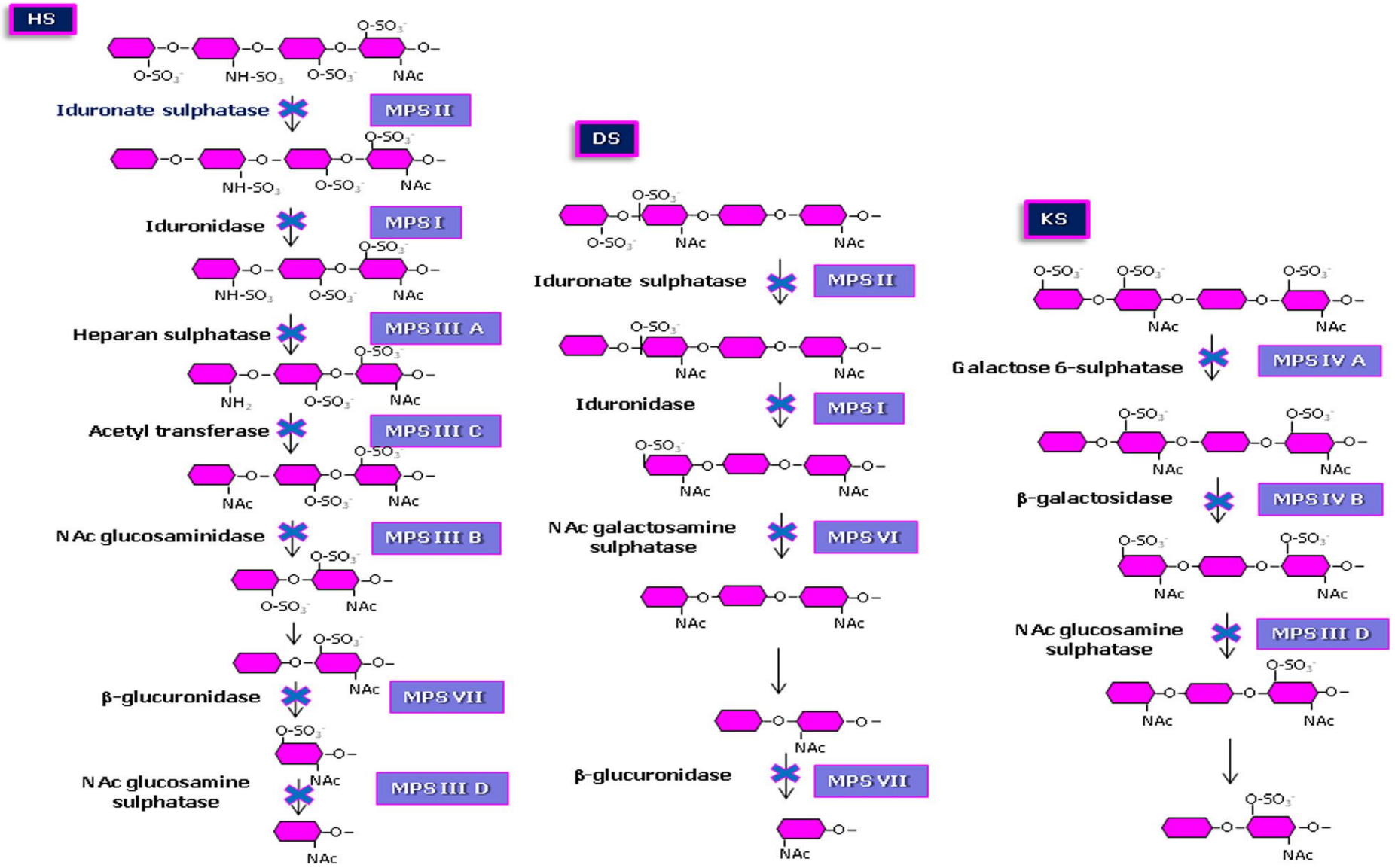
B-3- Heparin

It is also called α-Heparin. It is an anticoagulant present in liver and it is produced mainly by most cells of liver (Originally isolated from liver). In addition, it is also found in lungs, thymus, and spleen, walls of large arteries, skin and in small quantities in blood.

Structure: It is a polymer of repeating disaccharide units of D-Glucosamine and either of the two uronic acids-D-Glucuronic acid and L-Iduronic acid (see figure below). The -NH_2 group at C2 and OH group at C6 of D-Glucosamine (Glc N) are sulphated.



The degradation of the glycosaminoglycans (GAGs or mucopolysaccharides), a major component of the extracellular matrix, joint fluid, and connective tissue, takes place in the lysosomes. Under physiological conditions, the main GAG chains- dermatan sulphate (DS), heparin sulphate (HS), keratan sulphate (KS), and chondroitin sulphate (CS) - are degraded by 11 lysosomal hydrolases through the sequential removal of monosaccharides followed by the removal of sulphate groups, resulting in the complete degradation of the polysaccharide to its individual components. The deficit of any one of the 11 acid hydrolase activities gives rise to the progressive accumulation of GAGs in most tissues and organ systems, as well as in urine. Figure 1 illustrates the stepwise degradation of the main GAG chains by specific enzymes, as well as the resulting 11 distinct types of mucopolysaccharidoses (MPS) depending on the enzyme deficiency (Lysosomal storage disease).


HS
Iduronate sulphatase
MPS II
Iduronidase
MPS I
Heparan sulphatase
MPS III A
Acetyl transferase
MPS III C
NAc glucosaminidase
MPS III B
β-glucuronidase
MPS VII
NAc glucosamine sulphatase
MPS III D
DS
Iduronate sulphatase
MPS II
Iduronidase
MPS I
NAc galactosamine sulphatase
MPS VI
β-glucuronidase
MPS VII
KS
Galactose 6-sulphatase
MPS IV A
β-galactosidase
MPS IV B
NAc glucosamine sulphatase
MPS III D

Mucopolysaccharidoses are storage diseases

Mucopolysaccharidosis (MPS) is a group of rare, hereditary and incurable "storage diseases." MPS is named after mucopolysaccharides (sugars bound to proteins), which are not broken down correctly in these diseases, causing the products of incomplete metabolism to accumulate in the body. The stored mucopolysaccharides, nowadays called glycosaminoglycans (GAGs), start to disrupt cellular functions. It is estimated that one in 25,000 newborn children has some type of mucopolysaccharidosis (an incidence of 1:25,000).

Sanfilippo Syndrome

Deficiency in one of the four enzymes:

1. Heparan N- sulfatase (type A)
2. Alpha-N- acetylglucosaminidase (type B)
3. Acetyl -Co Alpha- glucosaminide acetyltransferase (type C)
4. N- acetylglucosamine 6-sulfatase (type D)

Symptoms

• By one year of age signs and symptoms of the disorder become apparent.

• Affected systems include skeletal, neurologic, cardiovascular, hearing, digestive, vision and respiratory,

• Symptoms can be severe including joint deformities, deafness, blindness and significant developmental regression. Sleep disorders, Hyperactivity with aggressive behavior, Hirsutism , and Mild hepatosplenomegaly other symptoms.