"Glycosaminoglycans, Proteoglycans, and Glycoproteins"

I. Glycosaminoglycan (GAG) Overview

- Definition and Structure
    - Glycosaminoglycans (GAGs) are large complexes of negatively charged heteropolysaccharide chains.
- Association with Proteins
    - They are generally associated with a small amount of protein, forming structures known as proteoglycans.
    - Proteoglycans typically consist of up to 95% carbohydrate.
- Function in Ground Substance
    - 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.

- Contribution to Extracellular Matrix (ECM)
    - Ground substance, along with:
        - Fibrous structural proteins such as:
            - Collagen
            - Elastin
            - Fibrillin-1
        - Adhesive proteins such as:
            - Fibronectin
    - Together make up the extracellular matrix (ECM).

- Roles of Hydrated GAGs
    - Serve as a flexible support for the ECM.
    - Interact with:
        - Structural proteins
        - Adhesive proteins
    - Act as a molecular sieve, influencing movement of materials through the ECM.

- Role in Mucous Secretions
    - The viscous, lubricating properties of mucous secretions also result from the presence of GAGs.
    - This function led to the original naming of these compounds as mucopolysaccharides.

II. Structure of Glycosaminoglycans (GAGs)

A. Basic Composition

- GAGs are long, unbranched heteropolysaccharides.
- Composed of repeating disaccharide chains:
    - One sugar is an N-acetylated amino sugar, either:
        - N-acetylglucosamine (GlcNAc)
        - N-acetylgalactosamine (GalNAc)
    - The other sugar is an acidic sugar.
- Exception:
    - Keratan sulfate contains galactose instead of an acidic sugar.

B. Amino Sugar Component

- Amino sugar is either:
    - D-glucosamine
    - D-galactosamine

- Characteristics:
    - 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

C. Acidic Sugar Component

- Acidic sugar is either:
    - D-glucuronic acid
    - Or its C-5 epimer, L-iduronic acid

- These uronic sugars contain carboxyl groups:
    - Carboxyl groups are negatively charged at physiologic pH.
    - Along with sulfate groups ($-SO_4^{2-}$), they give GAGs their strongly negative nature.

A. Structure-Function Relationship

- High concentration of negative charges:
    - Repeating disaccharide chains tend to be extended in solution.
    - Chains repel each other.
    - Surrounded by a shell of water molecules.
- Physical behavior:
    - When brought together, GAG chains slide past each other, similar to two magnets with the same polarity.
    - This results in the slippery consistency of:
        - Mucous secretions
        - Synovial fluid
- Compression behavior:
    - When a solution containing GAGs is compressed, water is squeezed out.
    - GAGs are forced to occupy a smaller volume.
    - Upon release of compression:
        - GAGs spring back to original hydrated volume.
        - Due to repulsion of their negative charges.

- This property contributes to the resilience of:
    - Cartilage
    - Synovial fluid
    - Vitreous humor of the eye

B. Classification

- The six major types of GAGs are divided according to:
    - Monomeric composition
    - Type of glycosidic linkages
    - Degree and location of sulfate units

- All GAGs, except for hyaluronic acid:
    - Are sulfated
    - Are found covalently attached to protein, forming proteoglycan monomers

C. Proteoglycans

1. Location

- Proteoglycans are found in:
    - The extracellular matrix (ECM)
    - The outer surface of cells

2. 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
- Each GAG chain:
    - May be composed of up to 200 disaccharide units
    - Extends out from the core protein
    - Remains separated from each other due to charge repulsion
- The overall structure resembles a bottle brush
- In cartilage proteoglycans, the main types of GAGs are:
    - Chondroitin sulfate
    - Keratan sulfate
- Proteoglycans are grouped into gene families:
    - These families encode core proteins with common structural features

Example: The aggrecan family, which includes:

- Aggrecan
- Versican
- Neurocan
- Brevican
- This family is abundant in cartilage

3. GAGs-Protein Linkage

- GAGs are attached to the core protein via covalent linkage:
  - Most commonly through a trihexoside consisting of:
    - Galactose-Galactose-Xylose
  - Linked to a serine residue in the protein
- An O-glycosidic bond is formed:
  - Between the xylose and the hydroxyl group of the serine

Clinical Application: Proteoglycans, Cartilage, and Osteoarthritis

- Osteoarthritis affects millions of individuals worldwide
- In osteoarthritis:
    - Joint cartilage is degraded
    - Proteoglycans, which normally help cushion the joint, are lost
- Without cartilage resilience, the joint suffers:
    - Pain
    - Stiffness
    - Swelling
    - With progressive worsening of signs and symptoms
- Glucosamine and chondroitin:
    - Reported to:
        - Relieve pain
        - Stop progression of osteoarthritis
    - Available as over-the-counter dietary supplements in the United States

- Based on several well-controlled clinical studies:
    - Glucosamine sulfate (not glucosamine hydrochloride) and chondroitin sulfate:
        - May have a small to moderate effect in relieving symptoms of osteoarthritis

3. Aggregate Formation

- Many proteoglycan monomers can associate with one molecule of hyaluronic acid to form proteoglycan aggregates.

- This association:
    - Is not covalent
    - Occurs primarily through ionic interactions between:
        - The core protein
        - The hyaluronic acid

- The association is stabilized by additional small proteins called link proteins

III. Synthesis of GAGs

- Heteropolysaccharide chains are elongated by:
    - The sequential addition of alternating acidic and amino sugars
    - These sugars are donated primarily by their uridine diphosphate (UDP) derivatives
- The reactions are catalyzed by:
    - A family of specific glycosyltransferases
- Since GAGs are produced for export from the cell:
    - Their synthesis occurs primarily in the Golgi

A. Amino Sugar Synthesis

- Amino sugars are essential components of:
    - Glycoconjugates such as:
        - Proteoglycans
        - Glycoproteins
        - Glycolipids

- The synthetic pathway of amino sugars (hexosamines) is:
    - Very active in connective tissues
    - As much as 20% of glucose flows through this pathway

1. N-Acetylglucosamine (GlcNAc) and N-Acetylgalactosamine (GalNAc)

- The monosaccharide fructose 6-phosphate is the precursor of:
    - GlcNAc (N-acetylglucosamine)
    - GalNAc (N-acetylgalactosamine)

- Reaction sequence:
    - A hydroxyl group on fructose is replaced by the amide nitrogen of a glutamine
    - The resulting glucosamine 6-phosphate is then:
        - Acetylated
        - Isomerized
        - Activated, producing the nucleotide sugar UDP-GlcNAc

- UDP-GalNAc is generated by:
    - The epimerization of UDP-GlcNAc
- These nucleotide sugar forms of the amino sugars are used to:
    - Elongate the carbohydrate chains

2. N-Acetylneuraminic Acid (NANA)

- NANA is:
    - A nine-carbon, acidic monosaccharide
    - A member of the family of sialic acids
    - Each sialic acid is acylated at a different site
- NANA and other sialic acids are usually found as:
    - Terminal carbohydrate residues of:
        - Oligosaccharide side chains of glycoproteins
        - Glycolipids
        - Less frequently, of GAGs

- Immediate sources of carbons and nitrogens for NANA synthesis:
    - N-Acetylmannosamine 6-phosphate (derived from fructose 6-phosphate)
    - Phosphoenolpyruvate (an intermediate in glycolysis)
- Before NANA can be added to a growing oligosaccharide:
    - It must be activated to CMP-NANA (cytidine monophosphate-NANA) by:
        - Reacting with cytidine triphosphate (CTP)
        - Catalyzed by CMP-NANA synthetase
- CMP-NANA is the only nucleotide sugar in human metabolism in which:
    - The carrier nucleotide is a monophosphate, not a diphosphate

B. Acidic Sugar Synthesis

- D-Glucuronic acid:
    - Has the structure of glucose with an oxidized carbon 6:
        - ($-CH_2OH \rightarrow -COOH$)
    - Along with its C-5 epimer L-iduronic acid, is an essential component of GAGs

- Glucuronic acid is also required for the detoxification of lipophilic compounds, such as:
    - Bilirubin
    - Steroids
    - Many drugs, including statins

- Detoxification occurs through conjugation with glucuronate:
    - Known as 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)
- The uronic acid pathway also:
    - Provides a mechanism by which dietary D-xylulose can enter central metabolic pathways

1. Glucuronic Acid

- Glucuronic acid can be obtained:
    - In small amounts from the diet
    - From the lysosomal degradation of GAGs
- It can also be synthesized by the uronic acid pathway:
    - Glucose 1-phosphate reacts with uridine triphosphate (UTP)
    - Converted to UDP-glucose

    - Oxidation of UDP-glucose produces UDP-glucuronic acid
        - This is the form that supplies glucuronic acid for:
            - GAG synthesis
            - Glucuronidation

- End product of glucuronic acid metabolism in humans:

    - D-xylulose 5-phosphate
        - Can enter the pentose phosphate pathway
        - Produces glycolytic intermediates:
            - Glyceraldehyde 3-phosphate
            - Fructose 6-phosphate

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-sugar to the L-sugar

C. Core Protein Synthesis

- The core protein is:
    - Made by ribosomes on the rough endoplasmic reticulum (RER)
    - Enters the RER lumen
    - Moves to the Golgi, where it is glycosylated by:
        - Membrane-bound glycosyltransferases

D. Carbohydrate Chain Synthesis

- Carbohydrate chain formation is initiated by:
    - Synthesis of a short linker on the core protein
        - This is where carbohydrate chain synthesis will occur

- Most common linker:
    - A trihexoside, formed by:
        - Transfer of a xylose from UDP-xylose to the hydroxyl group of a serine (or threonine)
        - Catalyzed by xylosyltransferase

- Next steps:
    - Two galactose molecules are added
        - Completing the trihexoside
    - Followed by:
        - Sequential addition of alternating acidic and amino sugars
        - Epimerization of some D-glucuronyl to L-iduronyl residues

E. Sulfate Group Addition

- Sulfation of a GAG occurs:
    - After the monosaccharide to be sulfated has been incorporated into the growing carbohydrate chain
- Source of the sulfate:
    - 3′-Phosphoadenosyl-5′-phosphosulfate (PAPS):
        - A molecule of adenosine monophosphate with a sulfate group attached to the 5′-phosphate
- Sulfation reaction is catalyzed by:
    - Sulfotransferases

- Note:
    - PAPS is also the sulfur donor in glycosphingolipid synthesis

IV. Degradation

- GAGs are degraded in lysosomes, which contain:
    - Hydrolytic enzymes most active at a pH of ~5
    - As a group, these enzymes are called acid hydrolases

- Low pH optimum within lysosomes:
    - Serves as a protective mechanism
    - Prevents enzymes from destroying the cell if leakage into the cytosol occurs, where the pH is neutral

- Half-lives of GAGs:
    - Vary from minutes to months
    - Influenced by:
        - Type of GAG
        - Location in the body

A. GAGs and Phagocytosis

- Because GAGs are extracellular or cell-surface compounds, they must first be:
    - Engulfed by invagination of the cell membrane (phagocytosis)
    - This forms a vesicle containing the GAGs to be degraded
- The vesicle fuses with a lysosome:
    - Forms a single digestive vesicle
    - Within this, GAGs are efficiently degraded

B. Lysosomal Degradation

- Lysosomal degradation of GAGs:
    - Requires a large number of acid hydrolases for complete digestion

- Steps of degradation:

1st Step:

- Polysaccharide chains are cleaved by endoglycosidases
    - Produces oligosaccharides

2nd Step:

- Further degradation occurs sequentially from the nonreducing end of each chain
    - The last group added during synthesis is the first group removed
    - Removal is by action of sulfatases or exoglycosidases

- Examples of enzymes and the bonds they hydrolyze:

- Note:

    - Endoglycosidases and exoglycosidases are also involved in lysosomal degradation of glycoproteins and glycolipids
    - Deficiencies in these enzymes lead to:
        - Accumulation of partially degraded carbohydrates
        - Resulting in tissue damage

Clinical Insight: Multiple Sulfatase Deficiency (Austin Disease)

- Multiple sulfatase deficiency is a rare lysosomal storage disease

- In this disorder:

    - All sulfatases are nonfunctional
    - Caused by a defect in the formation of formylglycine
        - Formylglycine is an amino acid derivative required at the active site for enzymatic activity

V. Mucopolysaccharidoses

- Mucopolysaccharidoses (MPS):

    - Hereditary diseases
    - Occurrence: ~1:25,000 live births
    - Caused by deficiency of any one of the lysosomal hydrolases
        - These enzymes normally degrade:
            - Heparan sulfate
            - Dermatan sulfate
            - Keratan sulfate

- Disorder characteristics:
    - Progressive disorders
    - Characterized by lysosomal accumulation of GAGs in various tissues
    - Symptoms include:
        - Skeletal deformities
        - Extracellular matrix (ECM) deformities
        - Intellectual disability
- Inheritance:
    - All are autosomal-recessive disorders
    - Exception: Hunter syndrome has X-linked inheritance
- Clinical course:
    - Children homozygous for the disease appear normal at birth
    - Gradual deterioration over time
    - In severe deficiencies, death occurs in childhood
    - Currently no cure

- Diagnosis:
    - Incomplete lysosomal degradation leads to oligosaccharides in urine
    - Diagnosis based on:
        - Identifying the structure at the nonreducing end of the oligosaccharide
            - This residue would be the substrate for the missing enzyme
        - Confirmation by measuring the patient's cellular level of lysosomal hydrolases
- Treatment approaches:
    - Bone marrow and cord blood transplants:
        - Transplanted macrophages produce the enzymes that degrade GAGs
        - Used for Hurler and Hunter syndromes
        - Limited success
    - Enzyme replacement therapy:
        - Available for Hurler and Hunter syndromes
        - Does not prevent neurologic damage

VI. Glycoprotein Overview

- Definition:
    - Glycoproteins are proteins to which oligosaccharides (glycans) are covalently attached
    - Glycosylation = Most common posttranslational modification of proteins
    - Glycation = Nonenzymatic addition of carbohydrate to proteins

- Carbohydrate content:
    - Glycoproteins have highly variable amounts of carbohydrate
    - Typically much less carbohydrate than proteoglycans
        - Example:
            - Immunoglobulin G (IgG): contains <4% carbohydrate by mass
            - Aggrecan (a proteoglycan): contains >80% carbohydrate by mass

- Glycan structure in glycoproteins:
    - Glycans are usually:
        - Short: 2 to 10 sugar residues
        - Often branched, not linear
        - May or may not be negatively charged

- Functions of membrane-bound glycoproteins:
    - Participate in broad range of cellular phenomena:
        - Cell-surface recognition by other cells, hormones, and viruses
        - Cell-surface antigenicity (e.g., blood group antigens)
        - Components of the extracellular matrix (ECM)
        - Components of mucins of the gastrointestinal and urogenital tracts
            - Act as protective biologic lubricants

- Plasma glycoproteins:
    - Almost all globular proteins in human plasma are glycoproteins
    - Albumin is an exception (not a glycoprotein)

VII. Oligosaccharide Structure

- Glycan components of glycoproteins:
    - Generally branched heteropolymers
    - Composed primarily of D-hexoses
    - May also include:
        - Neuraminic acid (a nonose)
        - L-fucose (a 6-deoxyhexose)

A. Carbohydrate-Protein Linkage

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

B. N- and O-Linked Oligosaccharides

- A glycoprotein may contain:
    - Only one type of glycosidic linkage (N or O linked), or
    - Both types within the same molecule

1. O-linked:

- O-linked glycans may have:
    - One or more of a wide variety of sugars
    - Sugars arranged in linear or branched patterns

- Common locations:
    - Found in extracellular glycoproteins
    - Found as membrane glycoprotein components

- Example:
    - O-linked oligosaccharides on the surface of red blood cells help provide the ABO blood group determinants
        - GalNAc as terminal sugar → blood group A
        - Galactose as terminal sugar → blood group B
        - Neither GalNAc nor galactose present → blood group O

2. N-linked:

- N-linked glycans fall into two broad classes:
    - Complex oligosaccharides
    - High-mannose oligosaccharides

- Both classes contain the same pentasaccharide core

- Differences:
    - Complex oligosaccharides:
        - Contain a diverse group of additional sugars
        - Examples: GlcNAc, GalNAc, L-fucose, NANA
    - High-mannose oligosaccharides:
        - Contain primarily mannose

VIII. Glycoprotein Synthesis

- Proteins destined to function in the cytoplasm are synthesized on free cytosolic ribosomes.

- Proteins, including glycoproteins, destined for:

    - Cellular membranes
    - Lysosomes
    - Or to be exported from the cell
    - Are synthesized on ribosomes attached to the endoplasmic reticulum (ER)

- These proteins contain specific signal sequences that act as molecular addresses, targeting them to proper destinations.

- An N-terminal hydrophobic sequence:

    - Initially directs these proteins to the ER
    - Allows the growing polypeptide to be extruded into the lumen

- The proteins are then:

    - Transported via secretory vesicles to the Golgi, which acts as a sorting center

- In the Golgi:
    - Glycoproteins destined to be:
        - Secreted from the cell, or
        - Targeted for lysosomes
        - Are packaged into vesicles that:
            - Fuse with the plasma or lysosomal membrane
            - Release their contents
    - Glycoproteins destined to become components of the cell membrane:
        - Are integrated into the Golgi membrane
        - Golgi membrane buds off, forming vesicles
        - Vesicles add their membrane-bound glycoproteins to the cell membrane
        - Glycoproteins are oriented with the carbohydrate portion facing the outside of the cell

A. Carbohydrate Components

- Precursors of the carbohydrate components of glycoproteins are nucleotide sugars, including:
    - UDP-glucose
    - UDP-galactose

    - UDP-GlcNAc
    - UDP-GalNAc
    - GDP-mannose
    - GDP-L-fucose (synthesized from GDP-mannose)
    - CMP-NANA

- When acidic NANA is present, the oligosaccharide has a negative charge at physiologic pH

- Oligosaccharides are covalently attached to the side chains of specific amino acids in the protein

- The three-dimensional structure of the protein determines whether or not a specific amino acid is glycosylated

B. O-Linked Glycoprotein Synthesis

- Synthesis of O-linked glycoproteins is very similar to that of the GAGs.

- Steps:
    - First, the protein to which sugars are to be attached is:
        - Synthesized on the RER
        - Extruded into its lumen
    - Glycosylation begins with the transfer of GalNAc (from UDP-GalNAc) to the hydroxyl group of a specific serine or threonine residue.
    - The glycosyltransferases responsible for the stepwise synthesis (from individual sugars) of the oligosaccharides:
        - Are bound to the membranes of the Golgi
        - Act in a specific order
        - Do not use a template, unlike DNA, RNA, and protein synthesis
        - Instead, they recognize the actual structure of the growing oligosaccharide as the appropriate substrate

C. N-Linked Glycoprotein Synthesis

- Synthesis of N-linked glycoproteins occurs in the lumen of the RER

- Requires the participation of:
    - The phosphorylated form of dolichol (dolichol pyrophosphate), a lipid of the RER membrane
- The initial product is:
    - Processed in the RER
    - And in the Golgi

1. Dolichol-Linked Oligosaccharide Synthesis

- As with O-linked glycoproteins:
    - The protein is synthesized on the RER
    - It enters the RER lumen
- Difference:
    - The protein does not become glycosylated with individual sugars
    - Instead, a lipid-linked oligosaccharide is first constructed

- This lipid-linked oligosaccharide consists of:
    - Dolichol:
        - An RER membrane lipid
        - Made from an intermediate of cholesterol synthesis
    - Attached through a pyrophosphate linkage to an oligosaccharide containing:
        - GlcNAc
        - Mannose
        - Glucose

- Sugars are added sequentially to dolichol by membrane-bound glycosyltransferases:
    - First GlcNAc
    - Followed by mannose
    - Then glucose

- The entire 14-sugar oligosaccharide is then:
    - Transferred from dolichol to the amide nitrogen of an asparagine residue in the protein
    - This is catalyzed by protein-oligosaccharide transferase present in RER
    - (Note: The antibiotic Tunicamycin inhibits N-linked glycosylation.)

1. Congenital Disorders of Glycosylation (CDG)

- CDG are syndromes caused primarily by defects in N-linked glycosylation of proteins.

- Two types:

    - Type I: Defects in oligosaccharide assembly
    - Type II: Defects in oligosaccharide processing

2. N-Linked Oligosaccharide Processing

- After addition of the N-linked oligosaccharide to the protein:

    - It is processed by removal of specific mannosyl and glucosyl residues
    - This occurs as the glycoprotein moves through the RER

- Final processing in the Golgi:
    - Oligosaccharide chains are completed by the addition of various sugars, such as:
        - GlcNAc
        - GalNAc
        - Additional mannoses
        - Fucose or NANA as terminal groups
    - This produces a complex glycoprotein
- Alternative outcome:
    - Some oligosaccharides are not further processed
    - Resulting in branched, mannose-containing chains
    - These form a high-mannose glycoprotein
- Ultimate fate of N-linked glycoproteins is the same as O-linked glycoproteins:
    - Can be released by the cell
    - Can become part of a cell membrane
- Additional role:
    - N-linked glycoproteins can be targeted to lysosomes

3. Lysosomal Enzymes

- N-linked glycoproteins being processed in the Golgi can be phosphorylated on:
    - Carbon 6 of one or more mannosyl residues
- Phosphate donor:
    - UDP-GlcNAc
- Catalyzing enzyme:
    - Phosphotransferase
- Mannose 6-phosphate (M6P) pathway:
    - Receptors in the Golgi membrane bind the M6P residues
    - These tagged proteins are:
        - Packaged into vesicles
        - Sent to the lysosomes

Clinical Application: I-Cell Disease

Definition and Naming

- I-Cell disease is a rare lysosomal storage disease
- Named for the large inclusion bodies seen in the cells of affected patients

Molecular Defect

- Deficient enzyme: GlcNAc phosphotransferase
- Resulting effect: Mannose 6-phosphate (M6P) is not generated on proteins destined for lysosomes

Misrouting of Acid Hydrolases

- Lack of M6P on amino acid residues causes:
    - Precursor acid hydrolases to be misdirected
    - They are sent to the plasma membrane and secreted constitutively
    - Instead of being trafficked to lysosomes

Pathophysiology

- Consequences:
    - Acid hydrolases are absent in lysosomes
    - Macromolecule substrates accumulate in lysosomes
    - This accumulation generates the inclusion bodies characteristic of the disorder
- Biochemical findings:
    - High concentrations of lysosomal enzymes are found in:
        - Plasma
        - Urine
    - Indicates defective lysosomal targeting

Clinical Features

- Skeletal abnormalities
- Restricted joint movement
- Coarse (dysmorphic) facial features
- Severe psychomotor impairment

Classification

- Shares features with:
    - Mucopolysaccharidoses
    - Sphingolipidoses
- Therefore, also termed a mucolipidosis (ML II)

Prognosis

- No current cure
- Death typically occurs in early childhood due to cardiopulmonary complications

Milder Form

- Pseudo-Hurler polydystrophy (ML III):
    - A less severe form of I-cell disease
    - Caused by residual activity of the phosphotransferase
    - Clinically resembles a mild form of Hurler syndrome

IX. Lysosomal Glycoprotein Degradation

Degradation Mechanism

- Degradation of glycoproteins is similar to that of GAGs

- Lysosomal acid hydrolases involved are:

    - Specific for the removal of one component of the glycoprotein
    - Primarily exoenzymes
    - Function: Remove their respective groups in reverse order of incorporation (i.e., last on, first off)

Enzyme Dependency

- If any degradative enzyme is missing:

    - Degradation by other exoenzymes cannot proceed
    - Leads to accumulation of partially degraded structures in lysosomes

Glycoprotein Storage Diseases (Oligosaccharidoses)

- Group of very rare, autosomal-recessive diseases
- Caused by deficiency of any one of the degradative enzymes
- Result in lysosomal accumulation of partially degraded glycoprotein fragments

Example: α-Mannosidosis Type 3

- Caused by deficiency of α-mannosidase
- Severe, progressive, and fatal
- Clinical presentation:
    - Similar to Hurler syndrome
    - Also includes immune deficiency
- Urine contains mannose-rich oligosaccharide fragments
- Diagnosis is made by enzyme activity assay