Overview

1. Glucose conversion to pentoses & NADPH
   • Precursors of nucleic acids, ATP, NAD, FAD, CoA
2. Inter-conversion of C3, C4, C5, C6 & C7 saccharides
   • Glucose or fructose dietary input
   • Glycogen
3. Nucleotide-linked monosaccharides
   • Activated forms with high energy bonds for complex carbohydrate assembly
4. Complex Carbohydrates
   • Specific biological functions
   • Recognition markers
5. Glycoproteins
6. Proteoglycans
Mutarotation
Saccharides exist in closed and open configurations

D-Glucose

\[\text{β-form} \quad \leftrightarrow \quad \text{Dynamic reactive bond} \quad \leftrightarrow \quad \text{α-form}\]
Glucose conversion to pentoses & NADPH

Figure 16.1. Oxidative phase of the pentose phosphate pathway: Formation of pentose phosphate and NADPH.

Glucose 6-PO$_4$ Dehydrogenase Deficiency

- High frequency in African, Mediterranean and Asiatic populations – Confers resistance??
- X-linked (>300 variants)
- Hemolytic anemia (the breakdown of red blood cells) only when the patient is exposed to certain drugs, foods or the stress of infection.
Glucose 6-PO$_4$ Dehydrogenase Deficiency

Medications / foods that can cause hemolytic anemia:

- Antimalarial drugs
- Aspirin
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Quinidine (antiarrhythmic agent)
- Quinine
- Sulfonamides (antimicrobials, diuretics, anticonvulsants)
- Nitrofurantoin (treatment of urinary tract infections)
- Fava beans
Glucose 6-PO₄ Dehydrogenase Deficiency

- G6PD is critical to the production of NADPH
- NADPH is required for glutathione reductase, the enzyme that generates reduced glutathione (GSH).
- GSH is essential for protection against and repair of oxidative damage; drug clearance.
- G6PD catalyzes the only reaction that produces NADPH in mature red cells, which lack the TCA cycle.
Hexosamine biosynthesis

N-acetylglucosamine

Figure 16.2. Nonoxidative reactions of the pentose phosphate pathway: Interconversions of pentose phosphates.

Wernicke-Korsakoff Syndrome

Cause:
• Heavy, long-term alcohol use is the most common association with Wernicke-Korsakoff syndrome.
• Deficiency of thiamine (vitamin B-1)
• Reduced activity of transketolase (low affinity for thiamine pyrophosphate)

Symptoms:
• Paralysis of eye movements
• Ataxia
• Mental confusion
• Punctate hemorrhages affecting the gray matter
• Psychosis
Inter-conversion of C3, C4, C5, C6 & C7 saccharides

![Diagram showing inter-conversion of C3, C4, C5, C6 & C7 saccharides](image)

**Figure 16.3. Pentose phosphate pathway.**

Inter-conversion of C6 saccharides

Glycogen hydrolysis

Glycogen $\rightarrow$ Glucose-1-PO$_4$

$\alpha 1,6$ $\rightarrow$ ATP $\rightarrow$ ADP

$\alpha 1,4$
Figure 16.4. Pathways of formation of nucleotide-linked sugars and interconversion of some hexoses.
Nucleotide-linked monosaccharide interconversion

Figure 16.5. Conversion of glucose into galactose.
Figure 16.6. Formation of UDP-glucuronic acid from UDP-glucose.


Figure 16.7. Biosynthesis of D-glucuronic acid from glucose.

Figure 16.8. Glucuronic acid oxidation pathway.

• Through glucuronidation they convert many internal and exogenous toxins to nontoxic metabolites.

• UGTs are a family of enzymes concentrated in the hepatic endoplasmic reticulum; one UGT isoform, bilirubin-UGT1 (BUGT1) conjugates bilirubin and is essential for its excretion.

• Inherited BUGT deficiency causes jaundice.
Figure 16.9. Biosynthesis of CMP-N-acetylneuraminic acid.

Complex Carbohydrates: Variable structures yield great information content

Complex type N-linked oligosaccharide

NeuAc $\overset{6}{\text{Gal}} \overset{5}{\text{GlcNAc}} \overset{4}{\text{Man}}$

NeuAc $\overset{\text{Gal}}{\text{GlcNAc}}$ $\text{Man}^3$

NeuAc $\overset{\text{Gal}}{\text{GlcNAc}}$ $\overset{\text{Man}}{\text{GlcNAc}}^2 \overset{\text{GlcNAc}}{\text{Man}}^1 \overset{8}{\text{Asn}}$

NeuAc $\overset{6}{\text{Gal}} \overset{5}{\text{GlcNAc}} \overset{4}{\text{GlcNAc}}$

Also high mannose and hybrid N-linked oligosaccharide types
Complex Carbohydrates
Variable structures yield great information content

Gal(β1-3)GalNAc-ol

NeuNAc(α2-3)Gal(β1-3)GalNAc-ol

NeuNAc(α2-6)
NeuNAc(α2-3)Gal(β1-3)GalNAc-ol

NeuNAc(α2-3)Gal(β1-4)GlcNAc(β1-6)GalNAc-ol

NeuNAc(α2-3)Gal(β1-4)GlcNAc(β1-6)NeuNAc(α2-3)Gal(β1-3)GalNAc-ol

Typical O-linked oligosaccharides
Lipid or protein → Glc → Gal → GlcNAc → Gal → GalNAc → A antigen

GalNAc transferase

Lipid or protein → Glc → Gal → GlcNAc → Gal → Fuc → O antigen

Gal transferase

Lipid or protein → Glc → Gal → GlcNAc → Gal → Gal → Fuc → B antigen

Glc = Glucose
Gal = Galactose
GlcNAc = N-Acetylglucosamine
GalNAc = N-Acetylgalactosamine
Fuc = Fucose
Complex Carbohydrates
Glycoproteins

Figure 16.10. Structure of three major types of glycopeptide bond.

Complex Carbohydrates
Influence biological activity of glycoproteins because they are prominent extended structures
Figure 16.11. Biosynthesis of the oligosaccharide core in asparagine-N-acetylgalactosamine-linked glycoproteins.

Carbohydrate-Deficient Glycoprotein Syndrome (CDGS)

Congenital Disorders of Glycosylation Syndrome

A group of rare, autosomal recessive disorders that are caused by defects in N-linked glycosylation

Type I: Caused by deficiency of an enzyme that functions before the sugar molecule is attached to the protein (13 subtypes)

Type II: Caused by a metabolic failure after the sugar molecule is attached (5 subtypes)
CDGS Ia (Jaeken syndrome)

• Accounts for 70% of all CDGS cases
• Caused by mutation in the gene encoding phosphomannomutase-2 (PMM2) which catalyzes the isomerization of mannose 6-phosphate to mannose 1-phosphate
• Severe – usually presents in neonates
• 20% lethality in the first year of life
CDGS Ia (Jaeken syndrome)

• Central & peripheral nervous system, liver
• Psychomotor retardation
• Moderate to severe mental retardation; impaired coordination and balance due to underdevelopment of the cerebellum
• Impaired nerve transmission to the legs, resulting in progressive, severe muscle thinning and weakness
• Visual and/or hearing impairment
• Nipple retraction, and hypogonadism
CDGS Ib (Gastrointestinal type)
Saguenay-Lac Saunt-Jean Syndrome; SLSJ Syndrome, Mannose-phosphate Isomerase Deficiency

- Lack of significant central nervous system involvement (unlike most other CDGSs)
- Failure to thrive
- Chronic diarrhea and protein-losing enteropathy
- Coagulopathy
- Can be treated effectively with oral mannose supplementation, but can be fatal if untreated
Mannose Metabolism

Glucose $\xrightarrow{HK} \text{Glc-6-P}$

$\text{Fru-6-P}$

Mannose $\xrightarrow{HK} \text{Man-6-P}$ $\xrightarrow{\text{PMM2}} \text{Man-1-P} \xrightarrow{\text{PMM2}} \text{GDP-Man}$

Diet

Glycoproteins
CDGS IIc
Leukocyte Adhesion Deficiency II (LAD2)

- Caused by mutations in the SLC35C1 gene encodes a GDP-fucose transporter (FucT1)
- Lack of fucosylated glycoconjugates, including selectin ligands
- Immunodeficiency
- Severe mental and growth retardation
- Patients with some mutations can be treated effectively with fucose
Synthesis

Degradation
A Typical Asn-GlcNAc Complex-Type Oligosaccharide Structure

NeuAc$_6$ Gal$_5$ GlcNAc$_4$ Man$_3$ Man$_7$ GlcNAc$_2$ GlcNAc$_1$ Asn$_8$ Fuc
## Defects in Degradation of Asn-GlcNAC Type Glycoproteins

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deficient Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartylglycosylaminuria</td>
<td>4-L-Aspartylglycosylamine Amidohydrolase (2)</td>
</tr>
<tr>
<td>( \beta )-Mannosidosis</td>
<td>( \beta )-Mannosidase (7)</td>
</tr>
<tr>
<td>( \alpha )-Mannosidosis</td>
<td>( \alpha )-Mannosidase (3)</td>
</tr>
<tr>
<td>GM2 gangliosidosis variant O (Sandhoff-Jatzkewitz Disease)</td>
<td>( \beta )-N-Acetylhexosaminidases (4)</td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
<td>( \beta )-Galactosidase (5)</td>
</tr>
<tr>
<td>Mucolipidosis I (sialidosis)</td>
<td>Sialidase (6)</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>( \alpha )-Fucosidase (8)</td>
</tr>
</tbody>
</table>
## Enzymatic Defects in Degradation of Glycolipids

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deficient Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs</td>
<td>$\beta$-Hexosaminidase A</td>
</tr>
<tr>
<td>Sandhoff’s</td>
<td>$\beta$-Hexosaminidases A &amp; B</td>
</tr>
<tr>
<td>GM1 Gangliosidosis</td>
<td>$\beta$-Galactosidase</td>
</tr>
<tr>
<td>Sialidosis</td>
<td>Sialidase</td>
</tr>
<tr>
<td>Fabry’s</td>
<td>$\alpha$-Galactosidase</td>
</tr>
<tr>
<td>Gaucher’s</td>
<td>$\beta$-Glucocerebrosidase</td>
</tr>
<tr>
<td>Krabbe’s</td>
<td>$\beta$-Galactocerebrosidase</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>Arylsulfatase A</td>
</tr>
</tbody>
</table>
Proteoglycans
Glycosaminoglycan chains

$\beta 1,4$ glucuronic acid $\beta 1,3$ N-acetylglucosamine $\beta 1,4$

Hyaluronan

$\beta 1,4$ glucuronic acid $\beta 1,3$ N-acetylgalactosamine $\beta 1,4$

chondroitin
Proteoglycans
High fixed negative charge density

β 1,4 glucuronic acid β 1,3 N-acetyl galactosamine β 1,4

chondroitin-4-sulfate
Add sulfate to 4-position of N-acetyl galactosamine
(other sites for sulfation **)
Tetrasaccharide linkage common to CS, DS, & HS chains

Core Protein (ser-gly)

Trans-Golgi Network

Golgi (cis, medial, trans)

Late ER/early Golgi event

Tetrasaccharide linkage common to CS, DS, & HS chains

Figure 16.13. Synthesis of chondroitin sulfate proteoglycan.
Proteoglycans
Linkage Oligosaccharides

CS, DS, and HS

KS-II

KS-I

KS

N-linked

O-linked

xylose
galactose
glucuronic acid
glcNAc

N
M
F
S
P
galNAc
mannose
fucose
sialic acid
phosphate
Proteoglycans
Sulfation of Glycosaminoglycan chains requires nucleotide-linked sulfate

Figure 16.14. Biosynthesis of 3′-phosphoadenosine 5′-phosphosulfate (PAPS).

Proteoglycans
Glycosaminoglycan chains

Repeat unit of hyaluronic acid
Repeat unit of chondroitin 4-sulfate
Repeat unit of heparin
Repeat unit of keratan sulfate
Repeat unit of dermatan sulfate

Figure 16.12. Major repeat units of glycosaminoglycan chains.
Proteoglycans
Core protein-GAG types

Extracellular Matrix (ECM) Functions

Cell Membrane Functions

Intracellular Granule Functions
Proteoglycans
Aggrecan

Hyaluronan binding domain

Aggrecan
Cartilage proteoglycan
~100 CS chains, ~100 KS chains ("bottle brush")

M_r ~ 2.5 x 10^6 Da
Length ~ 0.5 µm
Aggregate: 1 hyaluronan + ~180 aggrecan monomers
Supramacromolecular complexes (5-8 μm length)
Chondrocyte

Biosynthesis site:
Hyaluronan at plasma membrane
Aggre can in golgi complex

*AA
PAP^S
UDP~^*hexNAc
PG
HA
Proteoglycans
Serglycin

Mast cell

Intracellular secretory granule
(functions to package and inactivate cationic secretory molecules such as histamine and proteases)
Chondrodystrophies Due to Sulfation Defects

Autosomal Recessive (mutations in sulfate transporter)

• Diastrophic dysplasia (DTD)
  Short stature, joint dysplasia, normal lifespan

• Atelostegogenesis type II (AOII)
  Perinatally lethal

• Achondrogenesis type 1B (ACG-1B)
  Extremely short extremities and trunk
Chondrodystrophies Due to Sulfation Defects

Defective Synthesis of PAPS

• Spondyloepimetaphyseal dysplasia
  Short, bowed legs, enlarged knee joints, degenerative joint disease

• Brachymorphic mouse
  Growth disorder, short trunk & limbs, small skull
BRACHYMORPHIC MOUSE (bm/bm)

Synthesis of sulfation cofactor, PAPS, (phosphoadenosinephosphosulfate) is impaired. In cells such as chondrocytes with high synthesis of sulfated proteoglycans, PAPS becomes limiting with resultant undersulfation of glycosaminoglycan chains (up to 15% in growth cartilages), and foreshortening of epiphyseal plates.
Mucopolysaccharidoses

• Group of inherited metabolic diseases caused by the absence or malfunctioning of enzymes needed to break down glycosaminoglycans (GAGs)

• Lysosomal storage diseases

• Over time, the partially degraded GAGs collect in the cells, blood, and connective tissues.

• *Progressive, permanent*, cellular damage that affects the individual's appearance, physical abilities, organ function, and, in most cases, mental development.

• 1/25,000 live births (autosomal recessive, X-linked)

• Enzyme replacement therapy??
Dermatan sulfate and Heparan sulfate

**DS**

\[ \text{IdUA}_2 \text{GalNAc}_4 \text{GlcUA}_4 \text{GalNAc} \]

\[ \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \]

**HS**

\[ \text{IdUA}_2 \text{GlcN}_7 \text{GlcUA}_5 \text{GlcNAc}_9 \]

\[ \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \]
## Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>PG</th>
<th>Deficient Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter’s</td>
<td>HS</td>
<td>Iduronate sulfatase (1)</td>
</tr>
<tr>
<td>Hurler-Scheie</td>
<td>DS</td>
<td>$\alpha$-L-Iduronidase (2)</td>
</tr>
<tr>
<td>Maroteaux-Lamy</td>
<td>HS/DS</td>
<td>$N$-acetylgalactosamine sulfatase (3)</td>
</tr>
<tr>
<td>Mucolipidosis VII</td>
<td>HS/DS</td>
<td>$\beta$-Glucuronidase (3)</td>
</tr>
</tbody>
</table>
# Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>PG</th>
<th>Deficient Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanfilippo’s type A</td>
<td>HS</td>
<td>Heparan sulfamidase (6)</td>
</tr>
<tr>
<td>Sanfilippo’s type B</td>
<td>HS</td>
<td>N-acetyl-glucosaminidase (9)</td>
</tr>
<tr>
<td>Sanfilippo’s type C</td>
<td>HS</td>
<td>Acetyl CoA:a-glucosaminide acetyl transferase</td>
</tr>
<tr>
<td>Sanfilippo’s type D</td>
<td>HS</td>
<td>N-Acetylglucosamine 6-sulfatase (8)</td>
</tr>
<tr>
<td>Morquio’s type A</td>
<td>KS/CS</td>
<td>Galactose–6-sulfatase</td>
</tr>
<tr>
<td>Morquio’s type B</td>
<td>KS</td>
<td>β-Galactosidase</td>
</tr>
</tbody>
</table>
## Classification of the mucopolysaccharide storage diseases

<table>
<thead>
<tr>
<th>Disorder (Syndromic Name)</th>
<th>Enzyme Defect</th>
<th>Facies</th>
<th>Neurologic</th>
<th>Dysostosis Multiplex</th>
<th>Corneal Clouding</th>
<th>Hepatosplenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS IH (Hurler)</td>
<td>á-L-Iduronidase</td>
<td>Coarse</td>
<td>Severe MR</td>
<td>+++</td>
<td>+++++</td>
<td>+++</td>
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<tr>
<td>MPS IH/S (Hurler-Scheie)</td>
<td>á-L-Iduronidase</td>
<td>Coarse</td>
<td>± MR CTS</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>MPS IS (Scheie)</td>
<td>á-L-Iduronidase</td>
<td>Normal</td>
<td>CTS</td>
<td>+</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>MPS IIA (Hunter)</td>
<td>Iduronate-2-sulfatase</td>
<td>Coarse</td>
<td>Severe MR</td>
<td>+++</td>
<td>O</td>
<td>±</td>
</tr>
<tr>
<td>MPS IIB (Hunter)</td>
<td>Iduronate-2-sulfatase</td>
<td>Normal-to-mild coarsening</td>
<td>CTS</td>
<td>+ to ++</td>
<td>O</td>
<td>+</td>
</tr>
<tr>
<td>MPS IIIA (Sanfilippo)</td>
<td>Heparan N-sulfatase</td>
<td>Mild coarsening</td>
<td>Severe MR</td>
<td>±</td>
<td>±</td>
<td>O</td>
</tr>
<tr>
<td>MPS IIIB (Sanfilippo)</td>
<td>á-N-Acetylgalactosaminidase</td>
<td>Mild Coarsening</td>
<td>Severe MR</td>
<td>±</td>
<td>±</td>
<td>O</td>
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<tr>
<td>MPS IIC (Sanfilippo)</td>
<td>Acetyl-CoA:á-glucosaminidase acetyltransferase</td>
<td>Mild Coarsening</td>
<td>Severe MR</td>
<td>±</td>
<td>±</td>
<td>O</td>
</tr>
<tr>
<td>MPS IIIID (Sanfilippo)</td>
<td>N-Acetylgalactosamine 6-sulfatase</td>
<td>Mild Coarsening</td>
<td>Severe MR</td>
<td>±</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>MPS IVA (Morquio)</td>
<td>N-Acetylgalactosamine 6-sulfatase</td>
<td>Mildly dysmorphic</td>
<td>Cervical compression myelopathy</td>
<td>+++: absent or hypoplastic odontoid process</td>
<td>±</td>
<td>O</td>
</tr>
<tr>
<td>MPS IVB (Morquio)</td>
<td>β-Galactosidase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS VI (Maroteaux-Lamy)</td>
<td>Acetyl-CoA:á-glucosaminidase acetyltransferase</td>
<td>Mild-to-moderate coarsening</td>
<td>± MR</td>
<td>++</td>
<td>++ to +++</td>
<td>±</td>
</tr>
<tr>
<td>MPS VII (Sly)</td>
<td>N-Acetylgalactosamine 6-sulfatase</td>
<td>Mild coarsening</td>
<td>Severe MR</td>
<td>++</td>
<td>Unknown</td>
<td>+</td>
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<tr>
<td>MPS IX</td>
<td>Hyaluronidase</td>
<td>Polyarthropathy</td>
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</tbody>
</table>
Hurler’s Syndrome (MPS I)

- Deficient $\alpha$-L-iduronidase (DS GAGS)
- Thick, coarse facial features with low nasal bridge
- Progressive deterioration, progressive mental retardation
- Dwarfism, joint problems, abnormal bones in the spine
- Cloudy corneas
- Deafness
- Heart valve problems
- Death often by the age of 10
Cloudy corneas

Joint problems

Normal nasal bridge
Low nasal bridge

Abnormal bones
Clinical appearance of mucopolysaccharide storage disorders: Hurler-Scheie disease
Hurler’s Syndrome (MPS I)

• Bone Marrow Transplant / Cord Blood Transplant
• Enzyme Replacement Therapy??
  – Somewhat effective for reducing non-neurological symptoms and pain
Hunter’s Syndrome (MPS II)

• X-linked, iduronate 2-sulfatase deficiency
• Tissue deposits and excessive urinary excretion of GAGs derived from HS and DS
• Dwarfism, abnormal bone formation, abnormal facies, hepatosplenomegaly, deafness, progressive cardiovascular problems, limited joint mobility, neurocognitive degeneration
• MPS IIA - progressive mental retardation and physical disability, death by age 15
• MPS IIB - mild form, survival to adulthood, minimal mental impairment
Clinical appearance of mucopolysaccharide storage disorders: Morquio disease type A
Overview

1. Glucose conversion to pentoses & NADPH
   • Precursors of nucleic acids, ATP, NAD, FAD, CoA

2. Inter-convertion of C3, C4, C5, C6 & C7 saccharides
   • Glucose or fructose dietary input
   • Glycogen

3. Nucleotide-linked monosaccharides
   • Activated forms with high energy bonds for complex carbohydrate assembly

4. Complex Carbohydrates
   • Specific biological functions
   • Recognition markers

5. Glycoproteins

6. Proteoglycans