Lecture 23 (11/11/24)

Carbohydrates

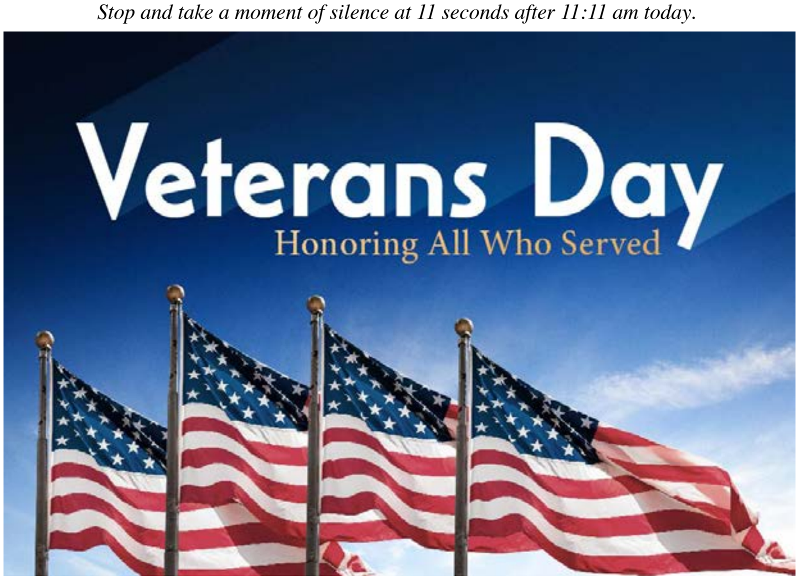
A. Definition
B. Roles
C. Monosaccharides-Chemistry
  1. Chirality
    a. One or more asymmetric carbons
    b. Linear and ring forms
  2. Derivatives: the chemistry of carbohydrates
    a. Oxidation
      i. C1
      ii. C6
    b. Reduction
      i. C1/C2
      ii. Other carbons
    c. Ester formation
    d. Amino sugars
  3. Polymerization
    a. The Glycosidic Bond
    b. Disaccharides
D. Oligosaccharides
  1. Glycoproteins & glycolipids
  2. O-linked
  3. N-linked
  4. Sequence determination-ABO
E. Polysaccharides
  1. Non-covalent bonds in macro-molecular structure
  2. Polymers of glucose
  3. Polymers of disaccharides

TODAY
- Reading: Ch7; 251-254, 258-260, 241-250
- Homework #21, 22

NEXT (Nucleic Acids)
- Reading: Ch8; 294-296, 263-269
  Ch24, 885-890
- Homework #23

11-11-2024

Stop and take a moment of silence at 11 seconds after 11:11 am today.



TODAY!!!!!   THANK A VET.

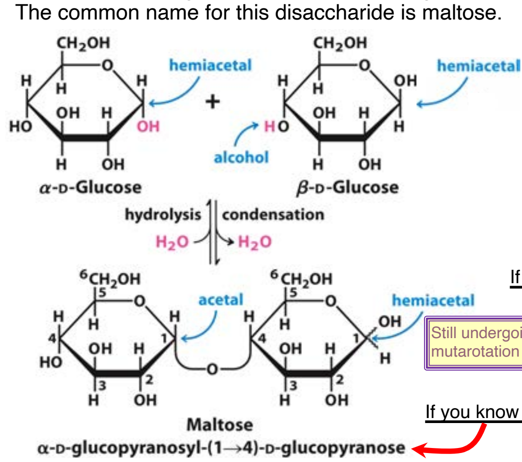
Carbohydrates

Disaccharides

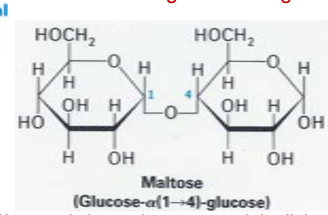
Carbohydrates

Disaccharides:

- Disaccharides can be named by the organization and linkage or a common name.
  - The disaccharide formed upon condensation of two glucose molecules via a 1 → 4 bond is described as α-D-glucopyranosyl-(1→4)-D-glucopyranose.
  - The common name for this disaccharide is maltose.



Non-reducing → reducing



If you only know the sugar and the linkage

Still undergoing mutarotation

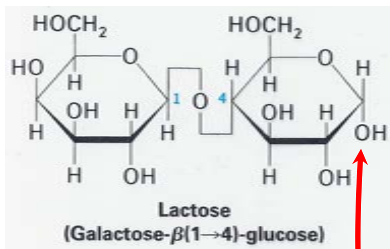
If you know the exact structure of the sugar

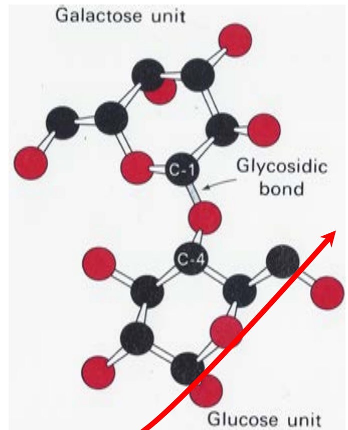
As we make sugar-polymers, the convention is to have the non-reducing sugar to the LEFT and the reducing end at the RIGHT.

Carbohydrates

Disaccharides:

Here is likely the first disaccharide you encountered in your life:
Lactose.





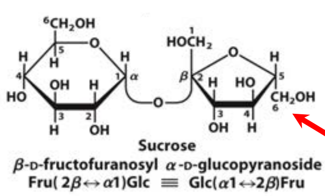
Non-reducing → reducing

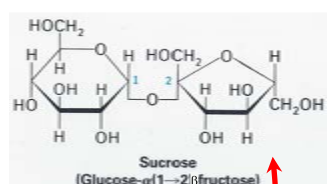
Still undergoing mutarotation

Carbohydrates

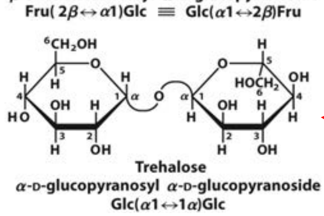
Disaccharides:

Here is likely the disaccharide you ingest the most:
Sucrose.





Trehalose



Notice that these are drawn upside down

Nonreducing Disaccharides

- Two sugar molecules can be also joined in a glycosidic bond between two anomeric carbons.
- The product has two acetal groups and no hemiacetals or hemiketals.
- There are no reducing ends; this is a nonreducing sugar.

Carbohydrates

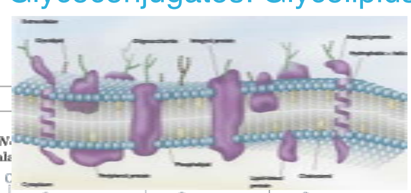
Oligosaccharides

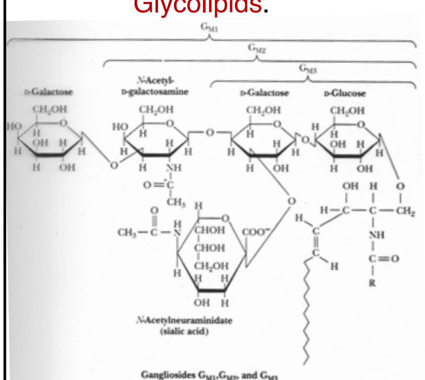
Carbohydrates

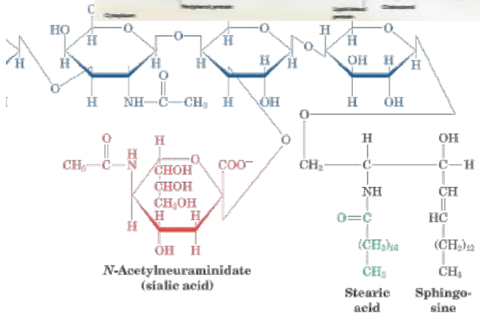
Oligosaccharides:

Here is an oligosaccharide that we encountered with sphingoglycolipids, or for short:
Glycolipids.

Glycoconjugates: Glycolipids



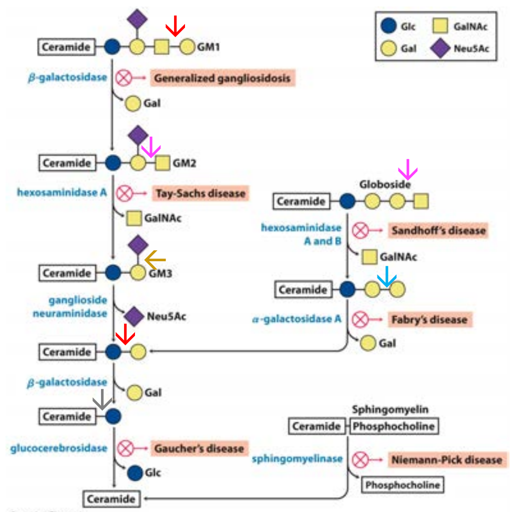




Ganglioside G_{M1}: structural formula with its sphingosine residue in Fischer projection (contain sialic acid)

GM1 = Gal-β(1→3)GalNAc-β(1→4)Gal-β(1→4)Glc-β(1→Ceramide)
Sia-β(2→3)

Dysfunction in Ganglioside Recycling Leads to a Variety of Medical Disorders



Box 10-1 Figure 1
Lehninger Principles of Biochemistry, Seventh Edition
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Individual enzymes specific for each type of glycosidic bond are needed to turn over oligosaccharides in the cell.

→ β-galactosidase

→ β-hexoaminidase

→ β-neuraminidase

→ β-gluco-ceramidase

→ α-galactosidase

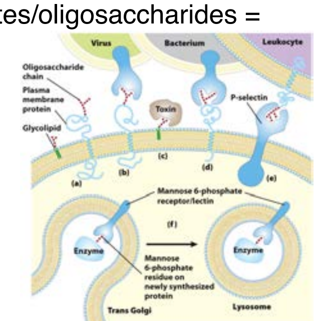
Carbohydrates

Oligosaccharides:

Glycoconjugates: Glycoprotein

When you attach an oligosaccharide to a protein: Glycoproteins.

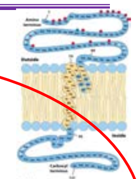
- A protein with small oligosaccharides attached:
  - Carbohydrate is attached via its anomeric carbon to amino acids on the protein.
    - Common connections occur at Ser, Thr, and Asn.
  - About half of mammalian proteins are glycoproteins.
  - Generally, bacteria do not glycosylate their proteins.
  - Carbohydrates play role in protein-protein recognition.
  - Viral proteins are heavily glycosylated; this helps evade the immune system.
- Proteins whose role is to bind specific carbohydrates/oligosaccharides = Lectins (or selectins)
  - Lectins important for many biological functions
    - Recruitment of leukocytes to sites of inflammation
    - Sperm-egg recognition
    - Virus-target cell interaction
    - Attachment of flora (microbiome) in gut
    - Nervous system development
    - Serum-protein turnover (sialic acid)
    - Targeting proteins to lysosomes for degradation (Man)



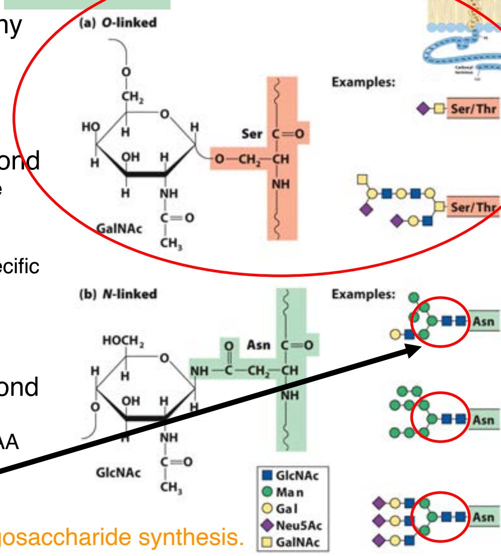
How are these sugars attached?

Carbohydrates

Oligosaccharides: TWO classes attached to proteins, O-linked and N-linked



- First, these polymers, unlike any others we have studies, are BRANCHED.
- Second, O-linked sugars are attached via an O-glycosidic bond
  - Use a Ser or Thr in the sequence (example: glycophorin)
  - Usually smaller than N-linked
  - Synthesized one at a time by specific glycosyltransferases (specific for sugar, linkage, and chirality)
- Third, N-linked sugars are attached via an N-glycosidic bond
  - Use an Asn
  - The Asn residues are within a 3 AA sequence context: NX$^S/_T$
  - All the same at the core



Let's look more closely at O-linked oligosaccharide synthesis.

Carbohydrates

Oligosaccharides: O- & N-linked

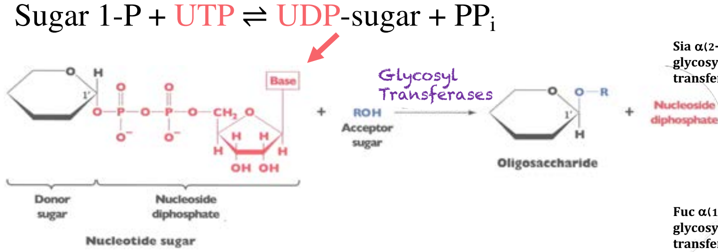
- Specific glycosyltransferases use "activated" sugars
- Activated by attaching to nucleotides: UDP, CDP, etc.

Kinase

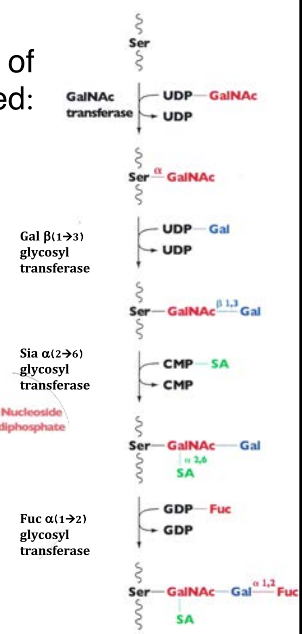
$$\text{Sugar} + \text{ATP} \rightleftharpoons \text{Sugar 1-P} + \text{ADP}$$

UDP-sugar pyrophosphorylase

$$\text{Sugar 1-P} + \text{UTP} \rightleftharpoons \text{UDP-sugar} + \text{PP}_i$$



EXAMPLE of O-linked:

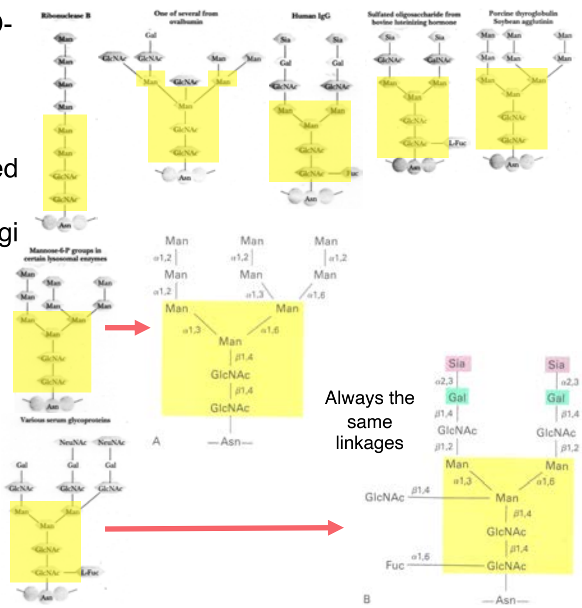


Both O- & N-linked biosynthesis uses these NDP-sugars

Carbohydrates

Oligosaccharides: N-linked

- Larger, more complex than O-linked
- All have a "Core" containing GlcNAc & Man
- Added as a unit, then modified before adding to Asn groups on proteins; all in the ER/Golgi
- Use an isoprene, called Dolichol, to build core
- Examples:

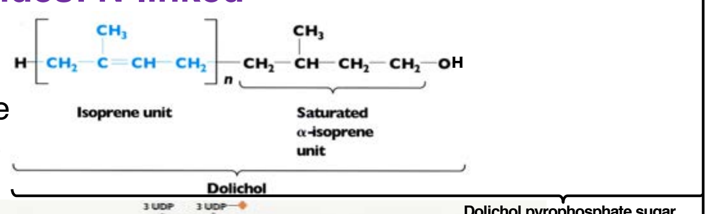


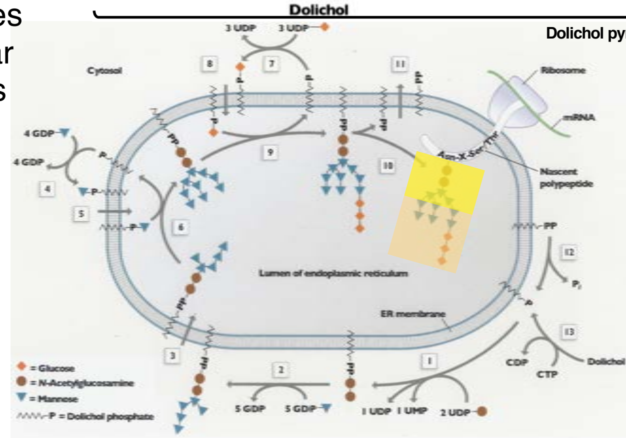
Let's look at this Dolichol & its use in biosynthesis more closely….

Carbohydrates

Oligosaccharides: N-linked

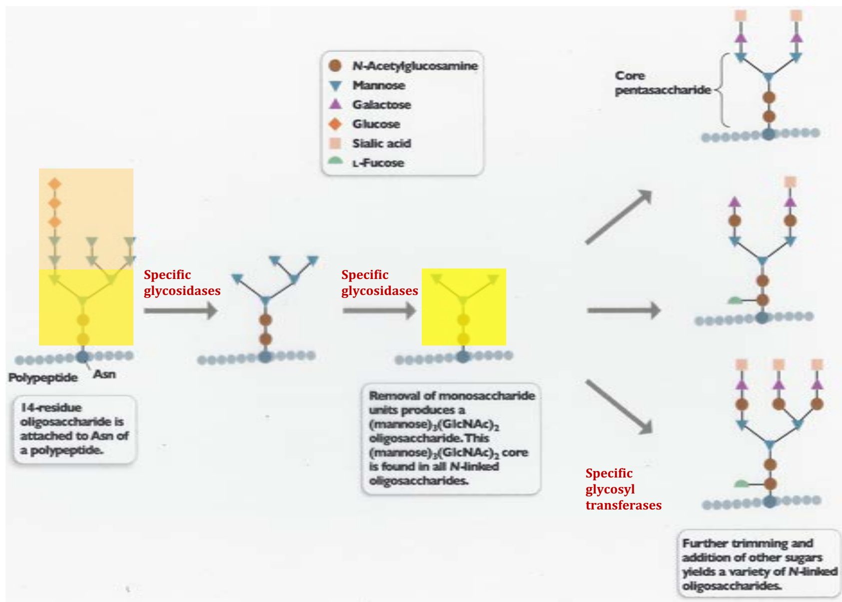
- Activated by attaching two phosphates, one using CTP (step 13)
- Again, uses NDP-sugar precursors





Carbohydrates

Oligosaccharides: N-linked



Carbohydrates

Oligosaccharides: Determination of Sequence

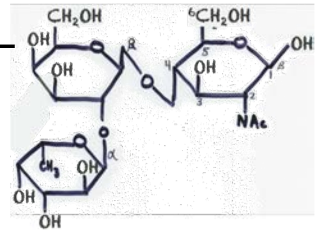
- Whole different problem compared to proteins and nucleic acids…. Its branched!!
- Moreover, a given residue can have several (and stereo-specific) ways of attaching to a neighboring residue.
- Need to use a combination of methods:
  - Chemical
    - Hydrolysis & chromatography to identify sugars
    - Exhaustive methylation & hydrolysis, then chromatography to identify what positions were not methylated
  - Biochemical
    - Use of enzymes that stereo-specifically hydrolyze glyosidic bonds (from the non-reducing end)

EXAMPLE: First, just like protein sequencing, you need to purify glyco-protein or lipid. Lets say we isolate the glycolipid from a person's RBC's who is O-positive. Treat it with a ceramidase to hydrolyze the lipid from the sugar.

Second, take an aliquot and just hydrolyze (like what was done for amino acid analysis). This gets the composition and stoichiometry.

Carbohydrates

Oligosaccharides: Determination of Sequence



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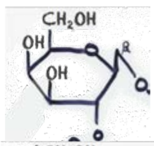
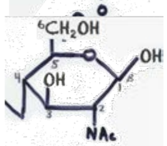
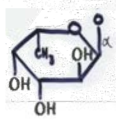


1 Gal



1 GlcNAc



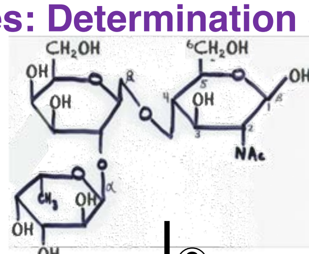
1 Fuc

① Chemical: Hydrolysis
② Chemical: Exhaustive methylation & hydrolysis
③ Biochemical: glyosidase

Carbohydrates

Oligosaccharides: Determination of Sequence

① Chemical: Hydrolysis
② Chemical: Exhaustive methylation & hydrolysis
③ Biochemical: glyosidase



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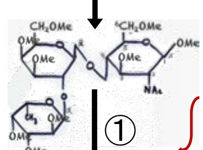

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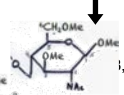
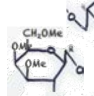


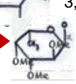
…,6 trimethyl-GlcNAc

- Methylation of C1-OH means it's a reducing carbon at the reducing end
- Lack of methylation of C4-OH means it was in glycosidic linkage with another sugar



3,4,6 trimethy-Gal

- Lack of methylation of C1-OH means its anomeric carbon was in a glycosidic bond
- Lack of methylation of C2-OH means that it was in glycosidic linkage with another sugar
- This sugar is in the middle

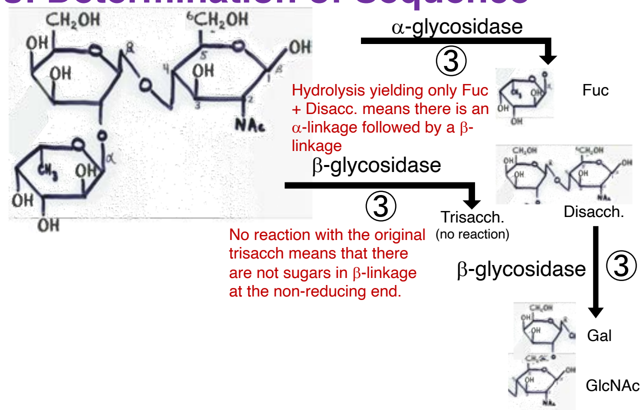


2,3,4 trimethyl-Fuc

- Again, lack of methylation of C1-OH.
- That all possible hydroxyls are methylated (recall Fuc is a 6-deoxy sugar); this sugar is at a non-reducing end (no other sugars attached to it)

Carbohydrates

Oligosaccharides: Determination of Sequence

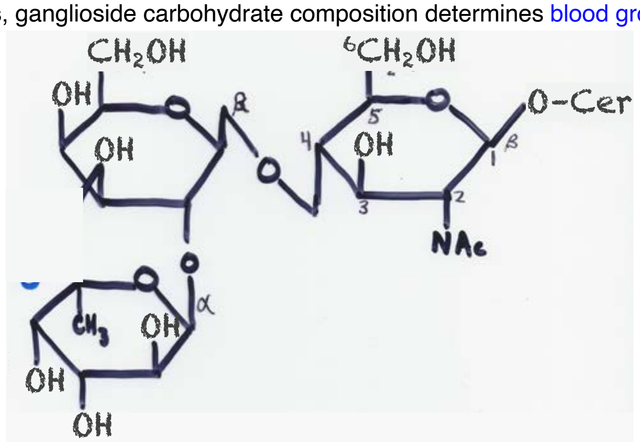


① Chemical: Hydrolysis
② Chemical: Exhaustive methylation & hydrolysis
③ Biochemical: glyosidase

Carbohydrates

Oligosaccharides: Determination of Sequence

– In vertebrates, ganglioside carbohydrate composition determines blood groups.



L-Fuc α(1→2)-D-Gal β(1→4) D-GlcNAc β-Ceramide — O blood group

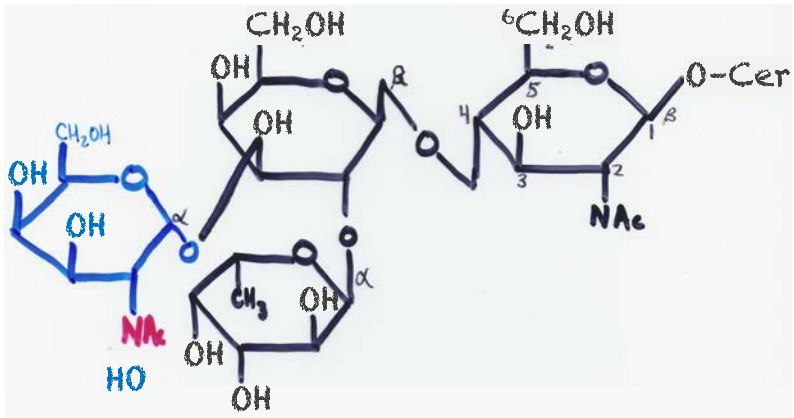
D-Gal α(1→3) — B blood group

D-GalNAc α(1→3) — A blood group

Carbohydrates

Oligosaccharides: Determination of Sequence

– In vertebrates, ganglioside carbohydrate composition determines blood groups.



L-Fuc α(1→2)-D-Gal β(1→4) D-GlcNAc β-Ceramide — O blood group

D-Gal α(1→3) — B blood group

D-GalNAc α(1→3) — A blood group

Glycoconjugates: Analysis

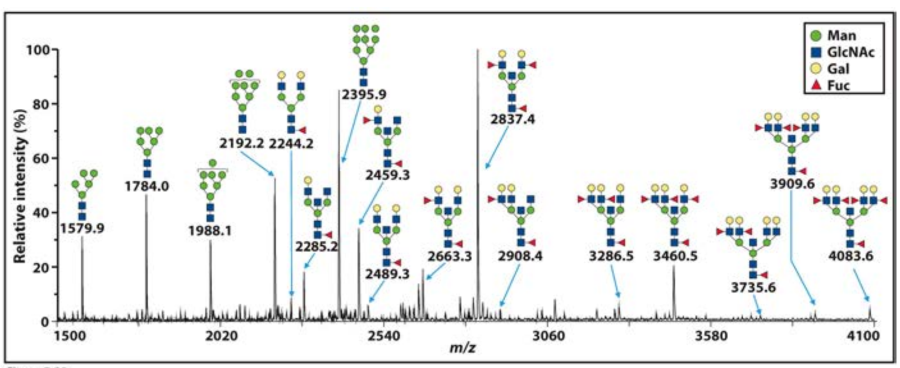


Figure 7-39
Lehninger Principles of Biochemistry, Seventh Edition

Carbohydrates

Polysaccharides

Carbohydrates

Polysaccharides

- The majority of natural carbohydrates are usually found as large polymers.
- These polysaccharides can be:
  - homopolysaccharides (one type of monomer unit*)
  - heteropolysaccharides (multiple types of monomer units)
  - linear (one type of glycosidic bond)
  - branched (multiple types of glycosidic bonds)
- Polysaccharides do not have a defined molecular weight.
  - This is in contrast to proteins because, unlike proteins, no template is used to make polysaccharides.
  - Polysaccharides are often in a state of flux; monomer units are added and removed as needed by the organism.

*monomer unit=monosaccharide

Carbohydrates

Polysaccharides: Polymers of Glucose

Homopolymers of Glucose:

- Starch
- Glycogen
- Cellulose
- Chitin

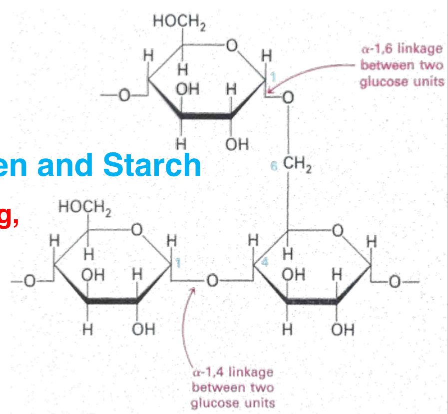
- Glycogen and Starch are the main storage polysaccharides for energy.
  - Glycogen and starch are insoluble due to their high molecular weight and often form granules in cells.
  - Molecular weight reaches several millions (~200 x 10^6)(can see in microscope).
- Glycogen is a branched homopolysaccharide of glucose.
  - Glucose monomers form $\alpha(1 \rightarrow 4)$ linked chains.
  - There are branch points with $\alpha(1 \rightarrow 6)$ linkers every 8–12 residues.
- Starch is a mixture of two homopolysaccharides of glucose.
  - Amylopectin is like glycogen, but the branch points ($\alpha(1 \rightarrow 6)$ linkages) occur every 24–30 residues.
  - Amylose is an unbranched polymer of $\alpha(1 \rightarrow 4)$ linked residues.

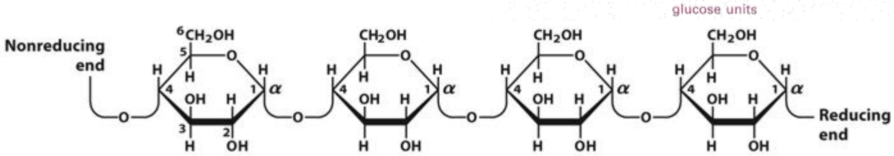
Carbohydrates

Polysaccharides: Glycogen & Starch

Glycosidic Linkages in Glycogen and Starch

(Glc-α(1→4)Glc)$_n$ with α(1→6) branching, where n≈10^6





Non-reducing → reducing

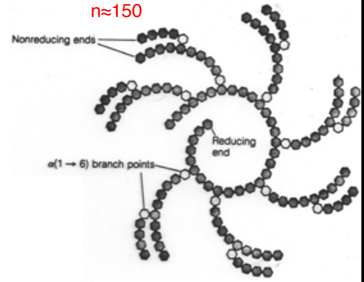
Haworth projections are not good to show the actual shape, which is helical!

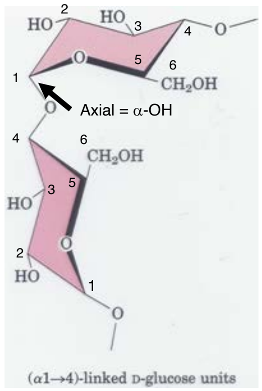
Carbohydrates

Polysaccharides: Glycogen & Starch

I_2

n≈150





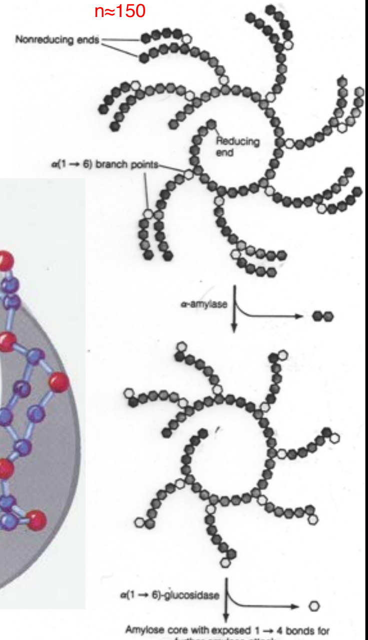
- Granules contain enzymes that synthesize and degrade these polymers.
- Glycogen and amylopectin have one reducing end but many nonreducing ends.
- Enzymatic processing occurs simultaneously in many nonreducing ends.

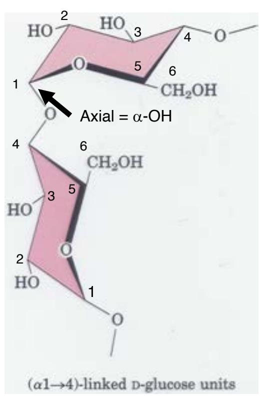
Carbohydrates

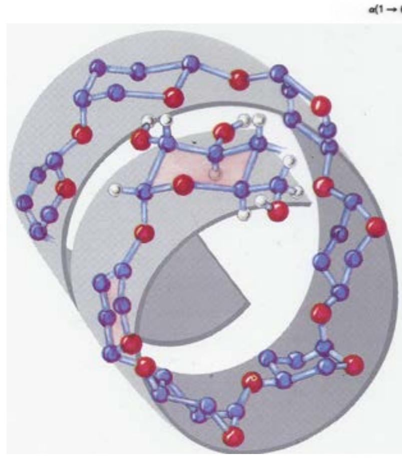
Polysaccharides: Glycogen & Starch

I_2

n≈150

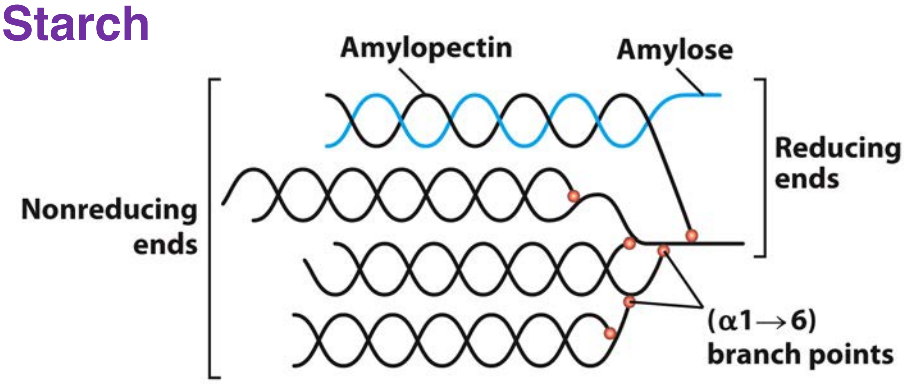






Carbohydrates

Polysaccharides: Glycogen & Starch



Mixture of **Amylose** and **Amylopectin** in Starch

Carbohydrates

Polysaccharides:

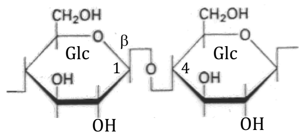
Homopolymers of Glucose:

- Starch
- Glycogen
- Cellulose
- Chitin

- Cellulose is a linear homopolysaccharide of glucose.
  - Glucose monomers form $\beta(1 \rightarrow 4)$ linked chains.
  - Hydrogen bonds form between adjacent monomers.
  - There are additional H-bonds between chains.
  - Structure is now tough and water insoluble.
  - It makes up almost 50% of plant mass; in cell walls.
  - Cotton is nearly pure fibrous cellulose.
- Chitin is a linear homopolysaccharide of *N*-acetylglucosamine (GlcNAc).
  - *N*-acetylglucosamine monomers form $\beta(1 \rightarrow 4)$-linked chains.
  - forms extended fibers that are similar to those of cellulose
  - hard, insoluble, cannot be digested by vertebrates
  - structure is tough but flexible, and water insoluble
  - found in cell walls in mushrooms and in exoskeletons of insects, spiders, crabs, and other arthropods

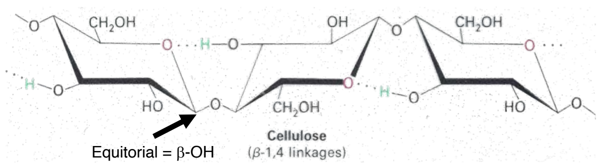
Carbohydrates

Polysaccharides: Cellulose & Chitin

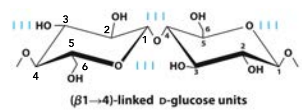


Glycosidic Linkages in Cellulose & Chitin

(Glc-β(1→4)Glc)$_n$ with NO branching, n ≈ 10^4



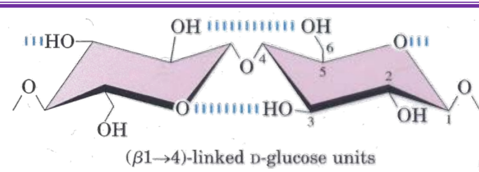
Notice that each chair is alternatively flipped

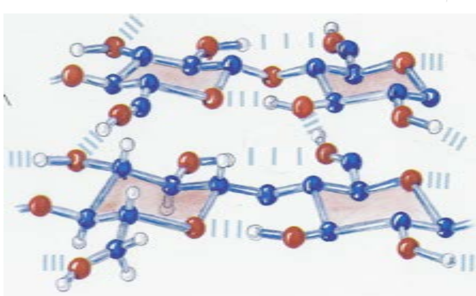


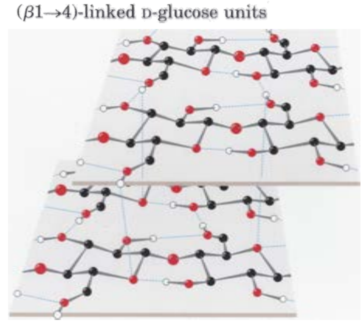
THE most abundant biological molecule in the world: ~300 trillion kg

Carbohydrates

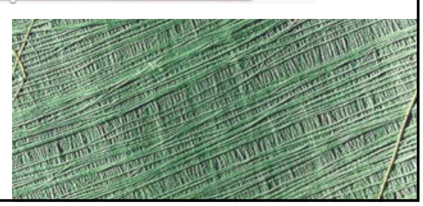
Polysaccharides: Cellulose & Chitin







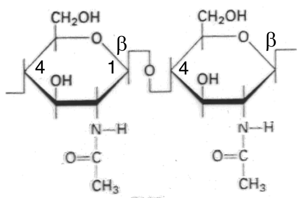
- The fibrous structure and water insolubility make cellulose a difficult substrate to act upon.
- Most animals cannot use cellulose as a fuel source because they lack the enzyme to hydrolyze β(1→4) linkages (β-Amylase or cellulase).
- Fungi, bacteria, and protozoa secrete cellulase, which allows them to use wood as source of glucose.
- Ruminants and termites live symbiotically with microorganisms that produce cellulase and are able to absorb the freed glucose into their bloodstreams.
- Cellulases hold promise in the fermentation of biomass into biofuels.



Carbohydrates

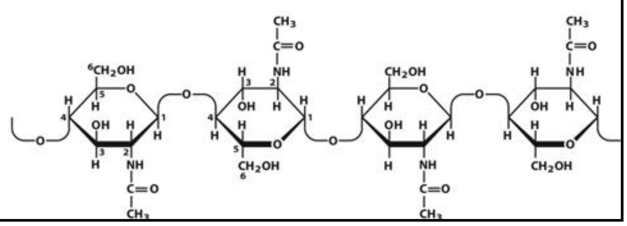
Polysaccharides: Cellulose & Chitin

A Sally lightfoot crab. The exoskeleton of this arthropod is rich in chitin, one of the most abundant biopolymers on earth.



Chitin

$(GlcNAc\text{-}\beta(1\rightarrow4)\text{-}GlcNAc)_n$

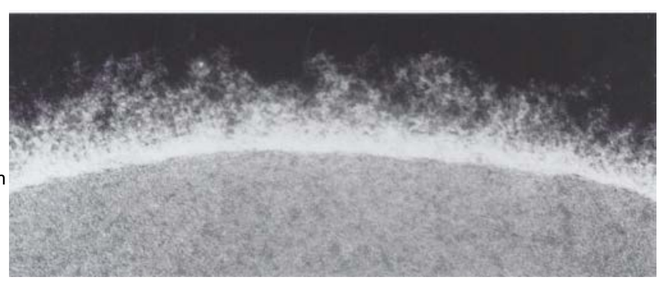


Carbohydrates

Polysaccharides: Polymers of Disaccharides

First, need to describe the Extracellular Matrix (ECM)

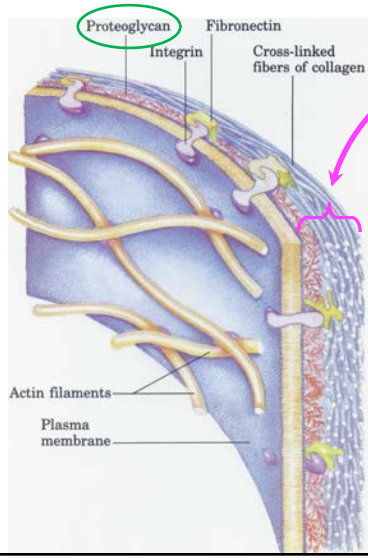
- Material outside the cell
- Strength, elasticity, and physical barrier in tissues (varies tremendously)
- Main components
  - proteoglycans
  - collagen & elastin fibers
- Proteoglycans
  - Different glycosaminoglycans are O-linked to the "core protein."
  - Linkage from anomeric carbon of xylose to serine hydroxyl
  - Our tissues have many different core proteins; aggrecan is the best studied.

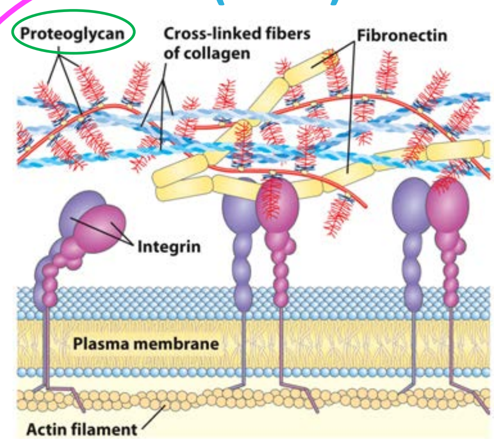


Carbohydrates

Polysaccharides: Polymers of Disaccharides

Extracellular Matrix (ECM)



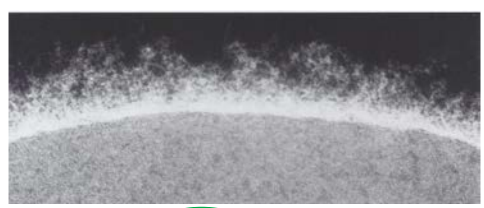


Carbohydrates

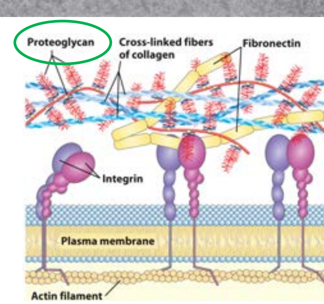
Polysaccharides: Polymers of Disaccharides

Extracellular Matrix (ECM)

- Main components
  - proteoglycans
  - collagen & elastin fibers



- Proteoglycans
  - Different glycosaminoglycans are O-linked to the "core protein."
- ECM is a barrier for tumor cells seeking to invade new tissues.
  - Some tumor cells secrete heparinase that degrades ECM.
- Cosmetics



Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

(the carbohydrate part of proteoglycans)

- Linear polymers of repeating disaccharide units $(\text{sugarX-sugarY})_n$
- One monomer (sugarX) is either sugar acid or Gal
  - uronic acids (C6 oxidation)
  - Most have sulfate esters
- One monomer (sugarY) is either:
  - *N*-acetyl-glucosamine (GlcNAc) or *N*-acetyl-galactosamine (GalNAc)
  - Also sulfate esters
- Extended hydrated molecule
  - Negatively charged
  - minimizes charge repulsion
- Forms meshwork with fibrous proteins to form extracellular matrix
  - connective tissue
  - lubrication of joints
- Form huge ($M_r > 2 \cdot 10^8$) noncovalent aggregates (Hyaluronan and Aggrecan).
  - They hold a lot of water (1000× its weight) and provide lubrication.
  - Very low friction material
  - Covers joint surfaces: articular cartilage
    - reduced friction & load balancing

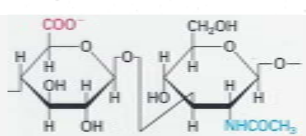
Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)

	Usual molecular weight of poly-saccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Hyaluronic acid[a]	$1 - 3 \times 10^6$	*N*-acetylglucosamine glucuronic acid	-	β-(1→4) β-(1→3)	synovial fluid, vitreous humor of the eye, umbilical cord, cock's comb



Hyaluronate

[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.

[b]This linkage of L-iduronic acid, identical to the β-linkage of D-glucuronic acid. However, iduronic acid is of the L rather than D configuration, which results in this bond being designated as α rather than β.

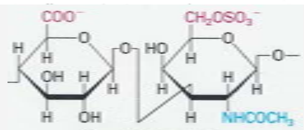
Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)

	Usual molecular weight of poly-saccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Chondroitin 4-sulfate (chondroitin sulfate A)	$2 - 5 \times 10^4$	N-acetylgalactosamine glucuronic acid	4	β-(1→4) β-(1→3)	human cartilage, aorta
Chondroitin 6-sulfate (chondroitin sulfate C)	$2 - 5 \times 10^4$	N-acetylgalactosamine glucuronic acid	6	β-(1→4) β-(1→3)	heart valves



Chondroitin 6-sulfate

[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.

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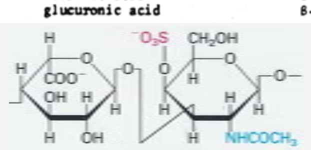
Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)

	Usual molecular weight of poly-saccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Dermatan sulfate (chondroitin sulfate B)	$2 - 5 \times 10^4$	N-acetylgalactosamine iduronic acid glucuronic acid	4	β-(1→4) α-(1→3)[b] β-(1→3)	skin, blood vessels, heart valves



Dermatan sulfate

[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.

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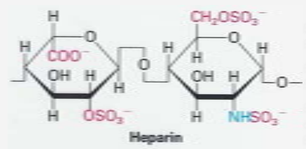
Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)



	Usual molecular weight of poly-saccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Heparin	$1 - 3 \times 10^4$	glucosamine glucuronic acid iduronic acid	3,6,N 2	α-(1→4) β-(1→4) α-(1→4)[b]	lung, mast cells
Heparan sulfate (heparitin sulfate)	$2 - 10 \times 10^3$	glucosamine *N*-acetylglucosamine glucuronic acid iduronic acid	N ? 3,6 2	 α-(1→4) β-(1→4) α-(1→4)[b]	blood vessels, cell surfaces

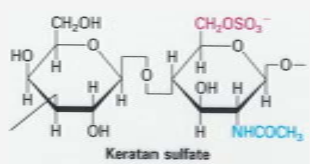
[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.
[b]This linkage of L-iduronic acid, identical to the β-linkage of D-glucuronic acid. However, iduronic acid is of the L rather than D configuration, which results in this bond being designated as α rather than β.

Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)



	Usual molecular weight of poly-saccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Keratan sulfate	$5 - 20 \times 10^3$	*N*-acetylglucosamine galactose	6 6	β-(1→3) β-(1→4)	cornea of the eye, nucleus pulposus, cartilage

[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.
[b]This linkage of L-iduronic acid, identical to the β-linkage of D-glucuronic acid. However, iduronic acid is of the L rather than D configuration, which results in this bond being designated as α rather than β.

Carbohydrates

Polysaccharides: Polymers of Disaccharides

Glycosaminoglycans

Major components of the polysaccharide portion of mucopolysaccharides (proteoglycans)

	Usual molecular weight of polysaccharide chain	Component sugars	Location of sulfate	Linkage	Major Source
Hyaluronic acid[a]	1 - 3 x 10^6	N-acetylglucosamine glucuronic acid	-	β-(1→4) β-(1→3)	synovial fluid, vitreous humor of the eye, umbilical cord, cock's comb
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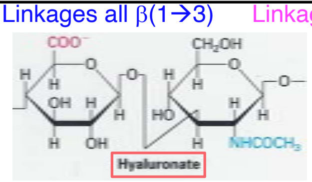
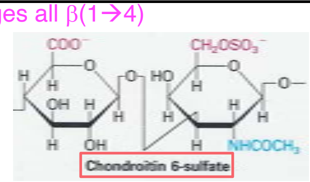
Chondroitin 6-sulfate (chondroitin sulfate C)	2 - 5 x 10^4	N-acetylgalactosamine glucuronic acid	6	β-(1→4) β-(1→3)	heart valves
Dermatan sulfate (chondroitin sulfate B)	2 - 5 x 10^4	N-acetylgalactosamine iduronic acid glucuronic acid	4	β-(1→4), α-(1→3)[b] β-(1→3)	skin, blood vessels, heart valves
Heparin	1 - 3 x 10^4	glucosamine glucuronic acid iduronic acid	3,6,N 2	α-(1→4) β-(1→4), α-(1→4)[b]	lung, mast cells
Heparan sulfate (heparitin sulfate)	2 - 10 x 10^3	glucosamine N-acetylglucosamine glucuronic acid iduronic acid	N ? 3,6 2	α-(1→4) β-(1→4) α-(1→4)[b]	blood vessels, cell surfaces
Keratan sulfate	5 - 20 x 10^3	N-acetylglucosamine galactose	6 6	β-(1→3) β-(1→4)	cornea of the eye, nucleus pulposus, cartilage

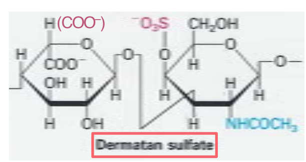
[a]The attachment of hyaluronic acid to protein has not been demonstrated unequivocally.

[b]This linkage of L-iduronic acid, identical to the β-linkage of D-glucuronic acid. However, iduronic acid is of the L rather than D configuration, which results in this bond being designated as α rather than β.

Linkages all β(1→3) Linkages all β(1→4)





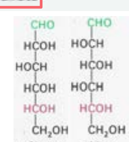


GlcUA – GlcNAc

GlcUA – GalNAc

C6/C4-sulfate

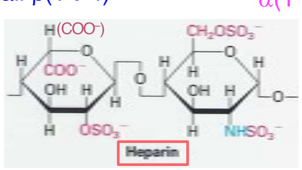
L-IdoUA (C5 epimer of D-Glc) & C4-sulfate only

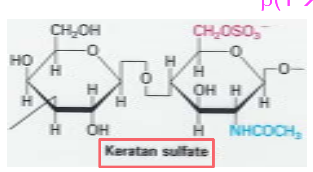


– (SugarX – SugarY)$_n$ –

GlcUA(IdoUA) or Gal GlcNAc or GalNAc or GlcN

Linkages all β(1→4) α(1→4) β(1→3)





GlcUA – GlcN

L-IdoUA GlcNAc

Sulfate everywhere, including GlcN

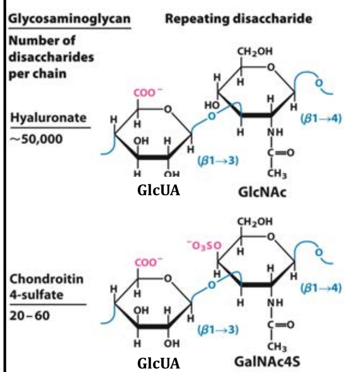
Gal – GlcNAc

C6-sulfate

Glycosaminoglycans

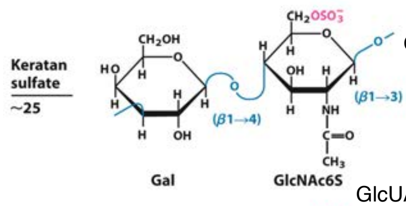
– (SugarX – SugarY)$_n$ –

GlcUA(IdoUA) or Gal — GlcNAc or GalNAc or GlcN



GlcUA – GlcNAc

GlcUA – GalNAc (C6/**C4**-sulfate)

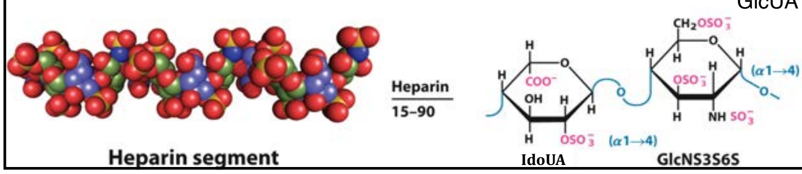


Gal – GlcNAc

C6-sulfate

Linkages all β, and opposite of Hyl & CS alternate (1→4) & (1→3)

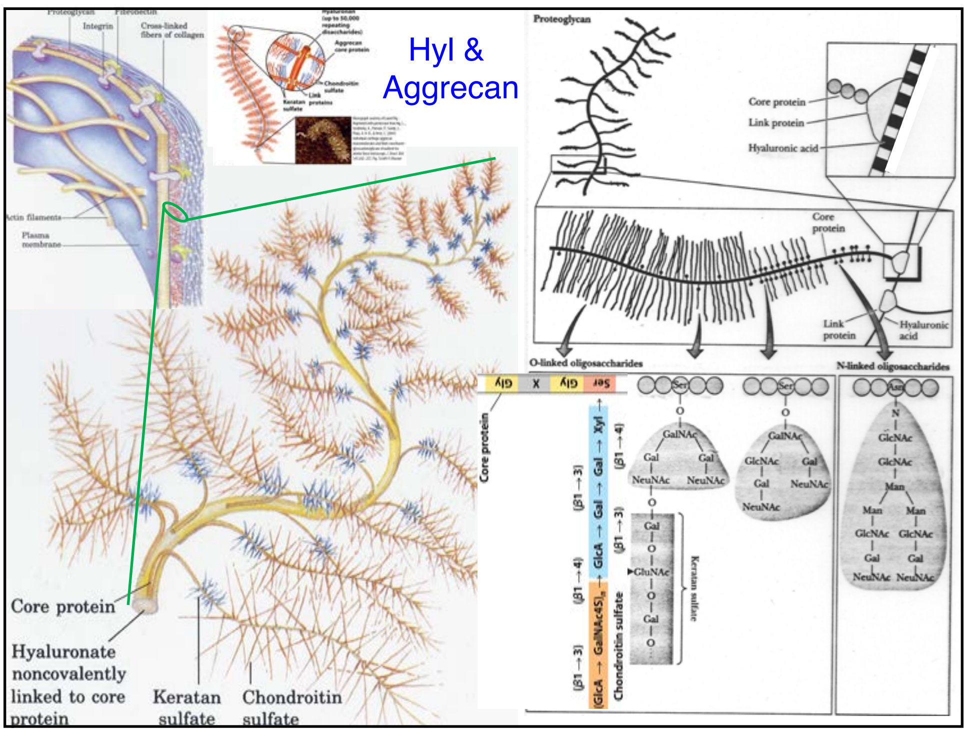
GlcUA or IdoUA – GlcN



Sulfate everywhere, including GlcN

Linkages all (1→4), alternate α & β

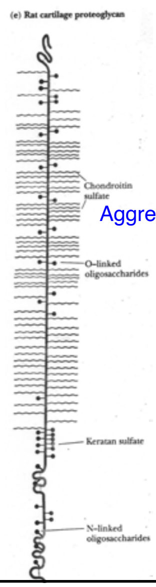
Hyl & Aggrecan



Carbohydrates

Polysaccharides: Proteoglycans = Polymers of Disaccharides (glycosaminoglycans) + proteins

a.k.a. - mucopolysaccharides



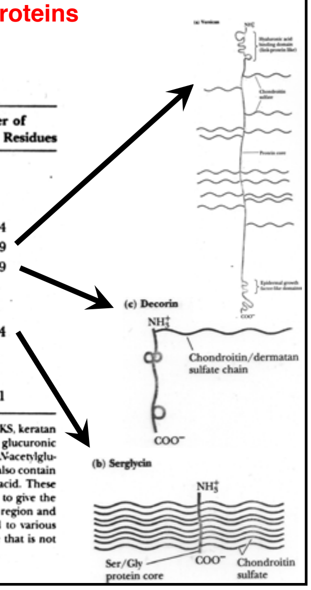
Aggrecan

Some Proteoglycans of Known Sequence

Proteoglycan	Glycosaminoglycan	Protein M_r	Number of Amino Acid Residues
Secreted or extracellular matrix proteoglycans			
Large aggregating cartilage proteoglycans	CS/KS*	220,952	2124
Versican	CS/DS	265,048	2409
Decorin	CS/DS	38,000	329
Intracellular granule proteoglycan			
Serglycin (PG19)	CS/DS	10,190	104
Membrane-intercalated proteoglycans			
Syndecan	HS/CS	38,868	311

*CS, chondroitin sulfate; DS, dermatan sulfate; HS, heparan sulfate (an analog of heparin); KS, keratan sulfate. These glycosaminoglycans are polymers consisting of the repeating disaccharides: glucuronic acid *N*-acetylgalactosamine (CS), iduronic acid *N*-acetylgalactosamine (DS), iduronic acid *N*-acetylglucosamine (HS and heparin), and galactose *N*-acetylglucosamine (KS). DS, HS, and heparin also contain some disaccharide units in which the uronic acid is glucuronic acid instead of iduronic acid. These glycosaminoglycans and CS are generally bound to the hydroxyl group of a serine residue to give the sequence (disaccharide) *n*GlcUA-Gal-Gal-Xyl-*O* Ser. Keratan sulfate has a different linkage region and can be either O- or N-linked. The sugars in the repeating disaccharide unit are sulfated to various degrees. By comparison, hyaluronic acid is a polymer of glucuronic acid and glucosamine that is not sulfated and does not attach covalently to a protein core.

Adapted from Ruoslahti, E., 1989. *Journal of Biological Chemistry* **264**:13369–13372.



Carbohydrates

Polysaccharides: Proteoglycans = Polymers of Disaccharides (glycosaminoglycans) + proteins

a.k.a. - mucopolysaccharides

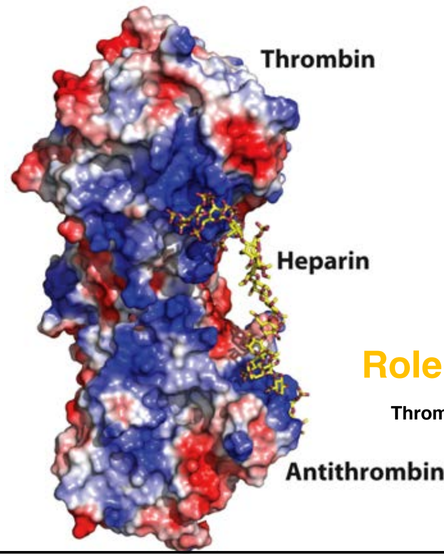
- Some integral membrane proteins are proteoglycans.
  - syndecans
- Other integral membrane proteins are receptors for extracellular proteoglycans.
  - Integrins (which then interact with Actin)
- These proteins link cellular cytoskeleton to the ECM and transmit signals into the cell to regulate:
  - cell growth
  - cell mobility
  - apoptosis
  - wound healing
- In chondrocytes, huge amounts of cartilage proteoglycans are produced (Aggrecan)
  - Resilience
  - Plasticity
  - Cushioning
  - Due to reversible hydration
- Heparin is linear polymer, 3–40 kDa.
  - Heparan sulfate is heparin-like polysaccharide but attached to proteins.
  - Highest density of negative-charge of any biomolecule
  - Prevent blood clotting by activating protease inhibitor antithrombin III
  - Binding to various cells regulates development and formation of blood vessels.
  - Modulates growth and development by binding growth-factor receptors
  - Important role in cancer metastasis
  - Can also bind to viruses and bacteria and decrease their virulence

Carbohydrates

Polysaccharides:

Proteoglycans = Polymers of Disaccharides (glycosaminoglycans) + proteins

a.k.a. - mucopolysaccharides



Thrombin activates the blood-clotting cascade by proteolysis

Anti-thrombin keeps thrombin inactive, preventing proteolysis

Prevent blood clotting by activating protease inhibitor anti-thrombin III

Role of Heparin

Thrombin + Anti-thrombin ⇌ Thrombin·Anti-thrombin

K_a is 1000 larger in presence of Heparin

→

TABLE 7-2 Structures and Roles of Some Polysaccharides

Primer	Type[a]	Repeating unit[b]	Size (number of monosaccharide units)	Roles/significance
Starch				Energy storage: in plants
Amylose	Homo-	(α1→4) Glc, linear	50–5,000	
Amylopectin	Homo-	(α1→4) Glc, with (α1→6) Glc branches every 24–30 residues	Up to 10^6	
Glycogen	Homo-	(α1→4) Glc, with (α1→6) Glc branches every 8–12 residues	Up to 50,000	Energy storage: in bacteria and animal cells
Cellulose	Homo-	(β1→4) Glc	Up to 15,000	Structural: in plants, gives rigidity and strength to cell walls
Chitin	Homo-	(β1→4) GlcNAc	Very large	Structural: in insects, spiders, crustaceans, gives rigidity and strength to exoskeletons
Peptidoglycan	Hetero-; peptides attached	4)Mur2Ac(β1→4) GlcNAc(β1	Very large	Structural: in bacteria, gives rigidity and strength to cell envelope
Hyaluronan (a glycosaminoglycan)	Hetero-; acidic	4)GlcA (β1→3) GlcNAc(β1	Up to 100,000	Structural: in vertebrates, extracellular matrix of skin and connective tissue; viscosity and lubrication in joints

[a]Each polymer is classified as a homopolysaccharide (homo-) or heteropolysaccharide (hetero-).
[b]The abbreviated names for the peptidoglycan, agarose, and hyaluronan repeating units indicate that the polymer contains repeats of this disaccharide unit. For example, in peptidoglycan, the GlcNAc of one disaccharide unit is (β1→4)-linked to the first residue of the next disaccharide unit.