

SYNTHESIS OF GLYCOPROTEINS

BIOCHEMISTRY

GLYCOPROTEINS

Introduction

Glycoproteins

- **Glycoproteins are proteins that contain oligosaccharide (glycan) chains covalently attached to their polypeptide backbones.**

- Almost all the **plasma proteins** of humans—except albumin—are glycoproteins.
- Many **proteins of cellular membranes** contain substantial amounts of carbohydrate.

- A number of the **blood group substances** are **glycoproteins**.
- Certain **hormones** (eg, chorionic gonadotropin) are **glycoproteins**.

- They differ from proteoglycans:
 - 1.Length of the chain is relatively short (usually 2-10 sugar residues) very long in GAGs.
 - 2.Do not have repeating disaccharide units.
 - 3.They are branched.
 - 4.May or may not be negatively charged.

- Glycoproteins occur in most organisms, from bacteria to humans.
- Their carbohydrate content ranges from 1% to over 85% by weight.
- They perform the following functions:

Function**Example**

Structural role

Collagen

Transport role

Transferrin

Immunologic role

Immunoglobulins

Cell-to-cell
communication

Selectins

Proteins in
fertilizationCell adhesion
molecules

Cell signalling

Many receptors

Clotting

Plasma proteins

Lipoproteins

Lubrication

Mucins

Hormones

HCG, TSH

Anti freeze

cold water fish

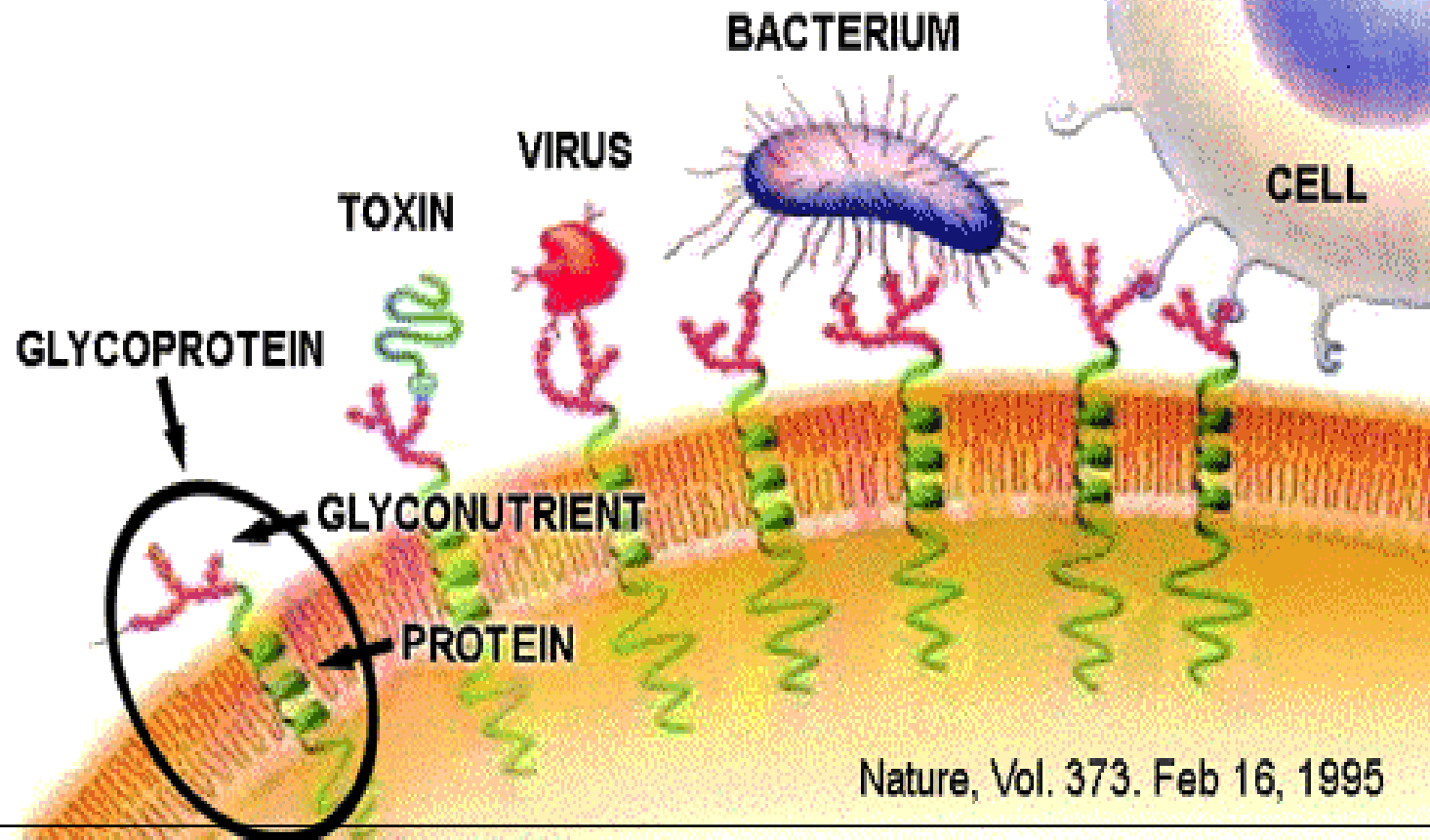
Some of the processes
involving glycoproteins:

- inflammation
- blood clotting
- peptic ulcers
- AIDS (HIV)

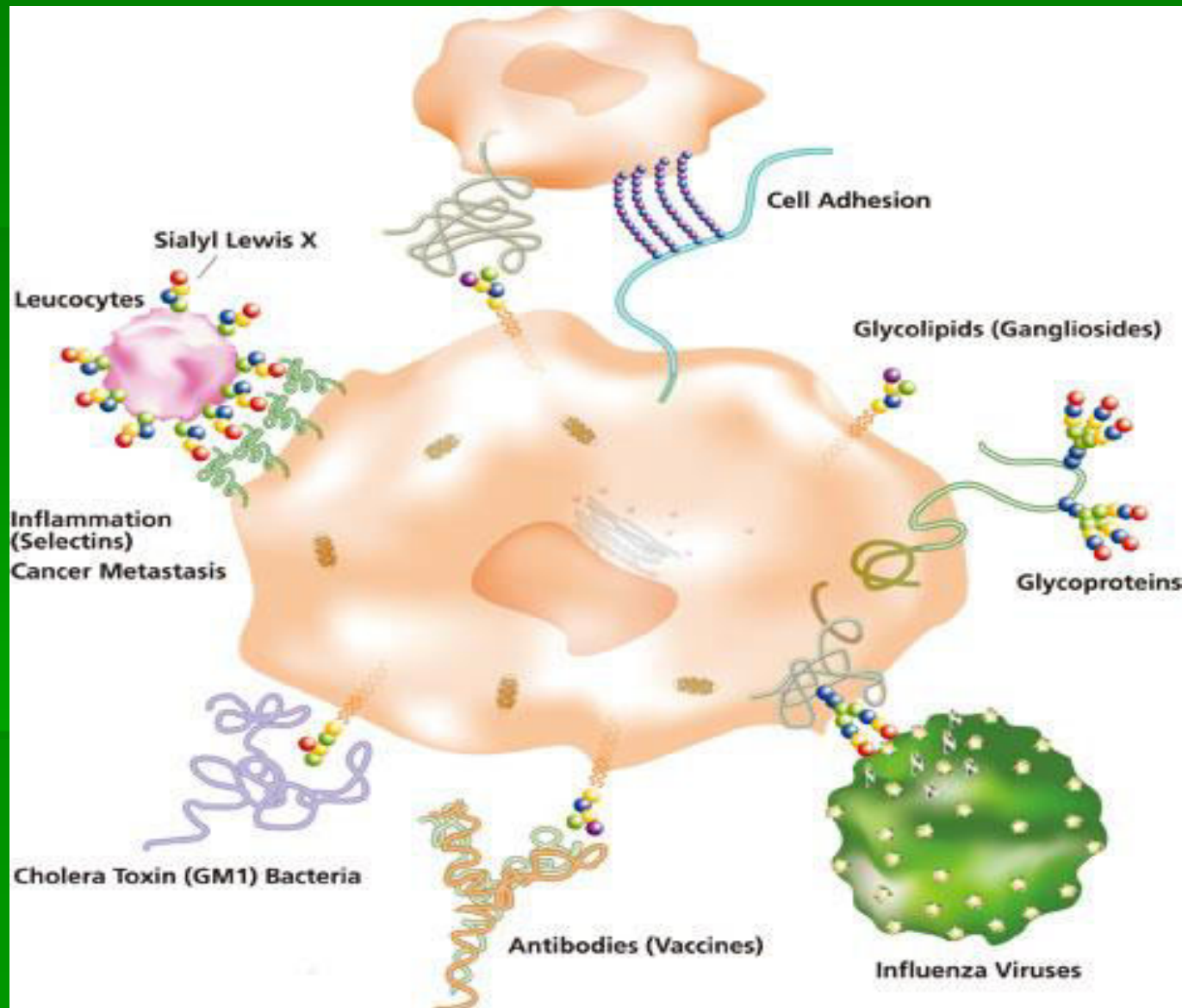
- influenza
- fertilization
- cancer
- cystic fibrosis
- arthritis

Glycoprotein Cell Receptors

Surface carbohydrates on cells serve as points of attachment for other cells, infectious bacteria, viruses, toxins, hormones and many other molecules.



Nature, Vol. 373. Feb 16, 1995



- The predominant sugars found in glycoproteins are:
- glucose (Glc),
- galactose (Gal),
- mannose (Man),
- fucose (Fuc),

- *N*-acetylgalactosamine (GalNAc),
- *N*-acetylglucosamine (GlcNAc)
- and *N*-acetylneuraminic acid (NANA).
NANA is also called sialic acid.

- The distinction between **proteoglycans** and **glycoproteins** resides in the level and types of carbohydrate modification.

- Proteoglycans also contain the sugar **glucuronic acid (GlcA)**.
- The carbohydrate modifications found in glycoproteins are rarely as complex as that of proteoglycans.

- The carbohydrates of glycoproteins are linked to the protein component through either **O-glycosidic** or **N-glycosidic** bonds.

- The **N-glycosidic** linkage is through the amide group of asparagine (Asn, N).
- The **O-glycosidic** linkage is to the hydroxyl of serine (Ser, S), threonine (Thr, T) or hydroxylysine (hLys).

O-linked sugars:

- May be membrane glycoprotein components
- Or extracellular glycoproteins.

- When attached to Ser or Thr, the sugar of O-linked glycoproteins is most often GalNAc.

- ***N*-linked sugars:** The predominant carbohydrate attachment in glycoproteins of mammalian cells is via *N*-glycosidic linkage.

They are of two types:

1. Complex oligosaccharides
2. High mannose oligosaccharides

- Their core pentasaccharide is the same.
- In the complex form additional sugar residues are present:
N-acetylglucosamine (GlcNAc)
and *N*-acetylneuraminic acid (NANA).
Fucose

- High mannose contain only mannose residues

- Most proteins that are secreted, or bound to the plasma membrane, are modified by carbohydrate attachment.
- The part that is modified, in plasma membrane-bound proteins, is the extracellular portion of the protein.

- Intracellular proteins are less frequently modified by carbohydrate attachment. However, the attachment of carbohydrate to intracellular proteins confers unique functional activities on these proteins

- I – cell disease
- Cancers
- Metastasis

Structure of Glycoprotein

- The oligosaccharide components of glycoproteins → is branched heteropolymers → composed of **D-hexoses**, with the addition in some cases of **neuraminic acid**, and of **L-fucose** (6-deoxyhexose)

N- and O-linked oligosaccharides

O-Linked oligosaccharides: found in **extracellular glycoproteins or as membrane glycoprotein components.**

- For example, O-linked oligosaccharides on the surface of RBCs help provide the **ABO blood group determinants**

N-linked oligosaccharides:

- two broad classes:
- 1. **complex oligosaccharides**
- 2. **high-mannose oligosaccharides.**

- Both contain the **same core pentasaccharide** but the **complex oligosaccharides** contain additional sugars,
 - for example; **N-acetylglucosamine (GlcNAc), L-fucose (Fuc), and N-acetylneuraminic acid (NANA)**
- The **high-mannose** oligosaccharides contain → **mannose**

Synthesis of O-linked glycosides

- The protein to which the oligosaccharides are to be attached is synthesized on the RER, and extruded into its lumen.
- Glycosylation begins with the transfer of **an N-acetylgalactosamine** (from UDP-N-acetylgalactosamine) onto a specific **seryl or threonyl R-group**

- The **glycosyl-transferases** responsible for the stepwise synthesis of the oligosaccharides are bound to the membranes of the Golgi apparatus.

Synthesis of the N-linked glycosides

- First, as with the O-linked glycosides, protein is synthesized on the RER and enters its lumen.
- The protein itself does not become glycosylated with individual sugars at this stage of glycoprotein synthesis, but rather a **lipid-linked oligosaccharide** is first constructed

- This consists of **dolichol** (an ER membrane lipid 80 to 100 carbons long) attached through a pyrophosphate linkage to an oligosaccharide containing **N-acetylglucosamine, mannose, and glucose.**

- The sugars to be added to the dolichol by the membrane-bound glycosyltransferases are **first N-acetylglucosamine, followed by mannose and glucose**

- The oligosaccharide is transferred from the dolichol to an **asparagine side** group of the protein by a protein-oligosaccharide **transferase** present in the ER.

Final processing of N-linked oligosaccharides

- After incorporation into the protein, the N-linked oligosaccharide is processed by the removal of specific mannosyl and glucosyl residues as the glycoprotein moves through the ER.

- Finally, the oligosaccharide chains are completed in the Golgi by addition of a variety of sugars (for example, N-acetylglucosamine, N-acetylgalactosamine, and additional mannoses, and then fucose or NANA as terminal groups)

- The ultimate fate of N-linked glycoproteins is the same as that of the O-linked, for example, they can be released by the cell, or become part of a cell membrane. In addition N-linked glycoproteins can be translocated to the lysosomes.

Enzymes destined for lysosomes

- N-linked glycoproteins being processed through the Golgi can be phosphorylated at one or more **specific mannosyl residues**.

- **Mannose 6-P receptors**, located in the Golgi apparatus, bind the mannose 6-P residues of these targeted enzymes, resulting in their translocation to the lysosomes

- **I-cell disease:**
 - rare syndrome
 - acid hydrolase enzymes normally found in lysosomes are absent,
 - results in an accumulation of substrates normally degraded by lysosomal enzymes within these vesicles.

- Individuals with I-cell disease:
 - are lacking the enzymic ability to **phosphorylate** the mannose residues of potential lysosomal enzymes, causing an **incorrect targeting** of these proteins to extracellular sites, rather than lysosomal vesicles

- I-cell disease is characterized by;
- **skeletal abnormalities**
- **restricted joint movement**
- **coarse facial features**
- **severe psychomotor impairment.**
- Death usually occurs by eight years of age.

- [Note: I-cell disease is considered to be a

Glyco-proteins

