# SYNTHESIS OF GLYCOPROTEINS

BIOCHEMISTRY

# Structure of Glycoprotein Oligosaccharides

- The oligosaccharide components of glycoproteins are generally branched heteropolymers composed primarily of:

- **D-hexoses**, with the addition in some cases of **neuraminic acid**, and of **L-fucose**—a 6-deoxyhexose.

# N- and O-linked oligosaccharides

**O-Linked oligosaccharides**:

- Many O-linked oligosaccharides are 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**:

- The N-linked oligosaccharides fall into two broad classes: **complex oligosaccharides** and **high-mannose oligosaccharides**.

- Both contain the **same core pentasaccharide** but the **complex oligosaccharides** contain a diverse group of additional sugars, for example, **N-acetylglucosamine (GlcNAc), L-fucose (Fuc), and N-acetylneuraminic acid (NANA)**

- The **high-mannose** oligosaccharides contain primarily **mannose** (Man).

# 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 **glycosyltransferases** 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** is a rare syndrome in which the acid hydrolase enzymes normally found in lysosomes are absent, resulting in an accumulation of substrates normally degraded by lysosomal enzymes within these vesicles.

- It has been determined that 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, and severe psychomotor impairment**. Death usually occurs by eight years of age.

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