The module: Molecules, Genes and Diseases (MGD)

Session 8

Lecture 13

Duration: 1 hour

Protein Processing in Cells; The Secretory Pathway

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Marks' Basic Medical Biochemistry Chapters 15, 26, 49
Medical Biochemistry Chapters 21, 28, 33
Lippincott's Illustrated Reviews: Biochemistry Chapters 4, 23, 31
Lippincott's Illustrated Reviews: Cell and Molecular Biology Chapter 11

For more detailed instruction, any question, cases need help please post to the group of session.

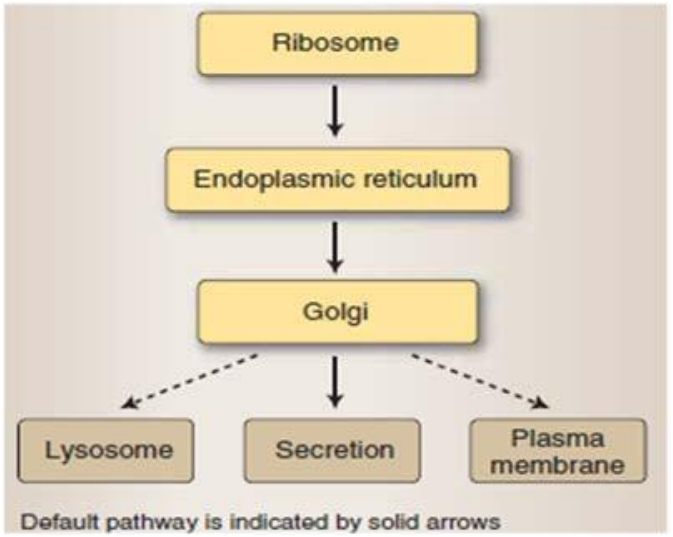
Intended learning outcomes of Lecture 13

At the end of this lecture you should be able to:

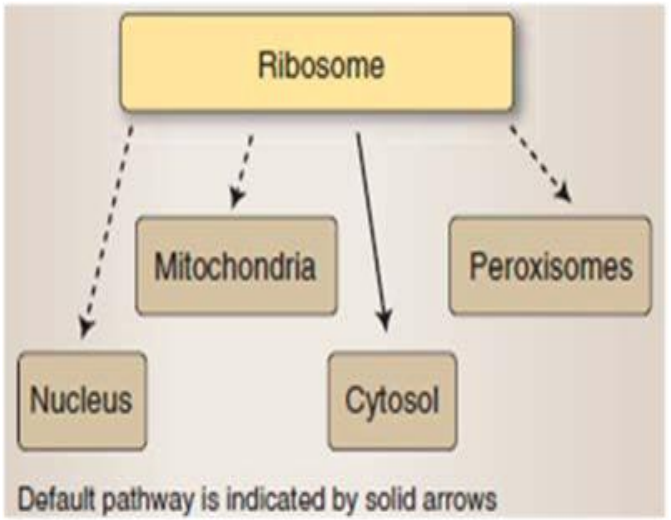
- Contrast the constitutive and regulated secretory pathways. (LO 8.1)
- Provide an overview of the secretory pathway in mammalian cells. (LO 8.2)
- List protein modifications which occur in the ER and Golgi complex. (LO 8.3)
- Distinguish between N-linked and O-linked glycosylation of proteins. (LO 8.4)
- Describe the role that proteolytic processing plays in the formation of important secreted proteins. (LO 8.5)

Contrast the constitutive and regulated secretory pathways (LO 8.1)

Most proteins that are destined for insertion into the plasma membrane, lysosomes, Golgi/ER or secretion are not synthesized on free ribosomes in the cytoplasm but are made on ribosomes **associated** with the endoplasmic reticulum (rough ER).



Proteins that will function in the nucleus, mitochondria, or peroxisomes are synthesized on **free** ribosomes.



Types of secretion:

(LO 8.1)

1. **Constitutive secretion**: (Continuous process)

- proteins packaged into vesicles and release continuously by exocytosis

e.g. serum albumin, collagen

2. Regulated secretion:

Proteins released in response to a signal e.g. hormone

-proteins packaged into vesicles but not released until stimulus received

e.g. insulin

(LO 8.1)

Secreted proteins have a **signal sequence** at the N-terminus that targets them to the ER. Signal sequences vary in length from 13-36 amino acids but typically contain:

- A stretch of ~10-15 hydrophobic residues.
- 1 or more positively charged residues near the amino terminus before the hydrophobic sequence.
- A few polar amino acids within the C-terminal region.
- A small, neutral side chain on the amino terminal side of the cleavage site. Alanine is most common.

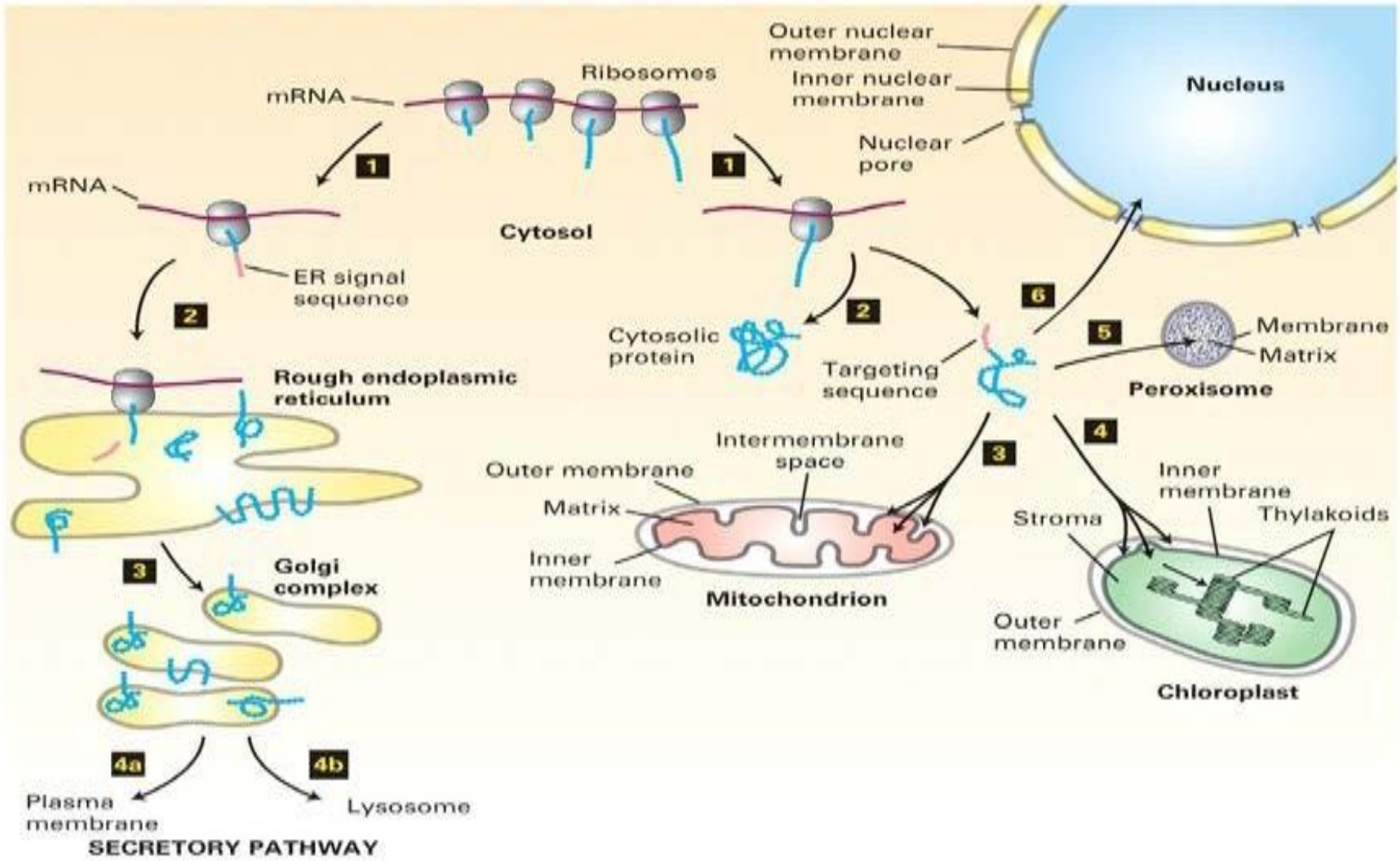
(LO 8.1)

A signal sequence on the growing polypeptide chain directs the ribosome to the ER membrane.

Signal sequences are absent from normally secreted proteins, because they are cleaved by signal peptidase on the luminal side of the ER membrane.

New proteins that leave the TGN (Trans Golgi Network) and not destined to function in lysosomes or to insert into plasma membrane will be secreted from the cell.

(LO 8.1)


mRNA
Ribosomes
1
mRNA
ER signal sequence
2
Rough endoplasmic reticulum
3
Golgi complex
4a
4b
Plasma membrane
Lysosome
SECRETORY PATHWAY
Cytosol
Outer nuclear membrane
Inner nuclear membrane
Nuclear pore
Nucleus
1
2
Cytosolic protein
Targeting sequence
6
5
Membrane
Matrix
Peroxisome
3
4
Outer membrane
Intermembrane space
Matrix
Inner membrane
Mitochondrion
Inner membrane
Stroma
Thylakoids
Outer membrane
Chloroplast

(LO 8.2)

The protein secretion pathway

1. Protein synthesis initiated on **free** ribosomes.

2. N-terminal **signal sequence** produced.

3. Signal sequence of newly formed protein is recognized by the **signal recognition particle** (SRP).

4. GTP-bound SRP directs the ribosome synthesizing the secretory protein to SRP receptors on the cytosolic face of the ER.

(LO 8.2)

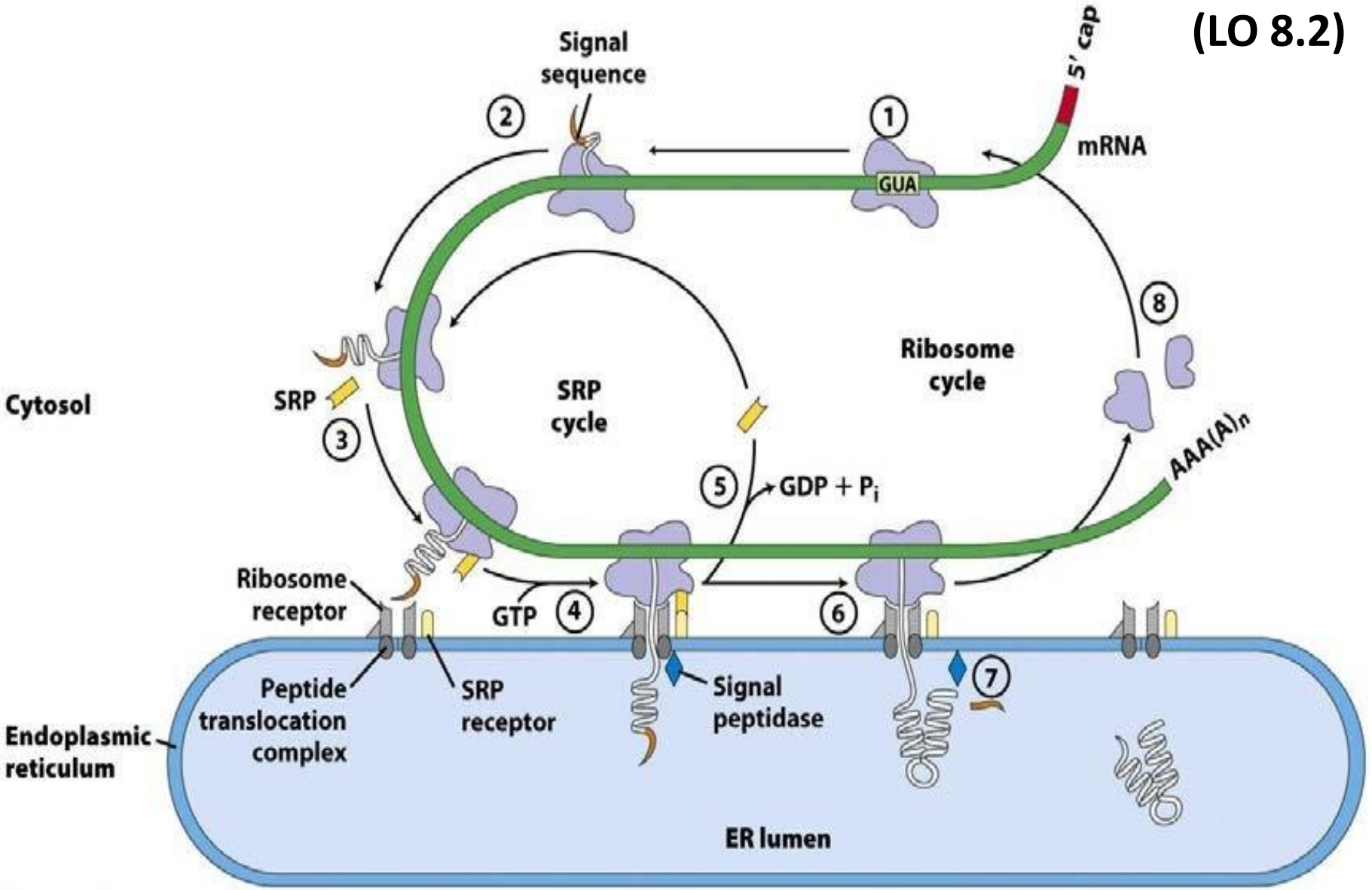
5. SRP dissociates.

6. Protein synthesis continues and the newly formed polypeptide is fed into the ER via a pore in the membrane (peptide translocation complex).

7. Signal sequence is removed by a **signal peptidase** once the entire protein has been synthesized.

8. The ribosome dissociates and is **recycled**.

(LO 8.2)


Signal sequence
5′ cap
mRNA
GUA
Cytosol
SRP
SRP cycle
Ribosome cycle
GDP + Pi
AAA(A)n
Ribosome receptor
GTP
Peptide translocation complex
SRP receptor
Signal peptidase
Endoplasmic reticulum
ER lumen

(LO 8.2)

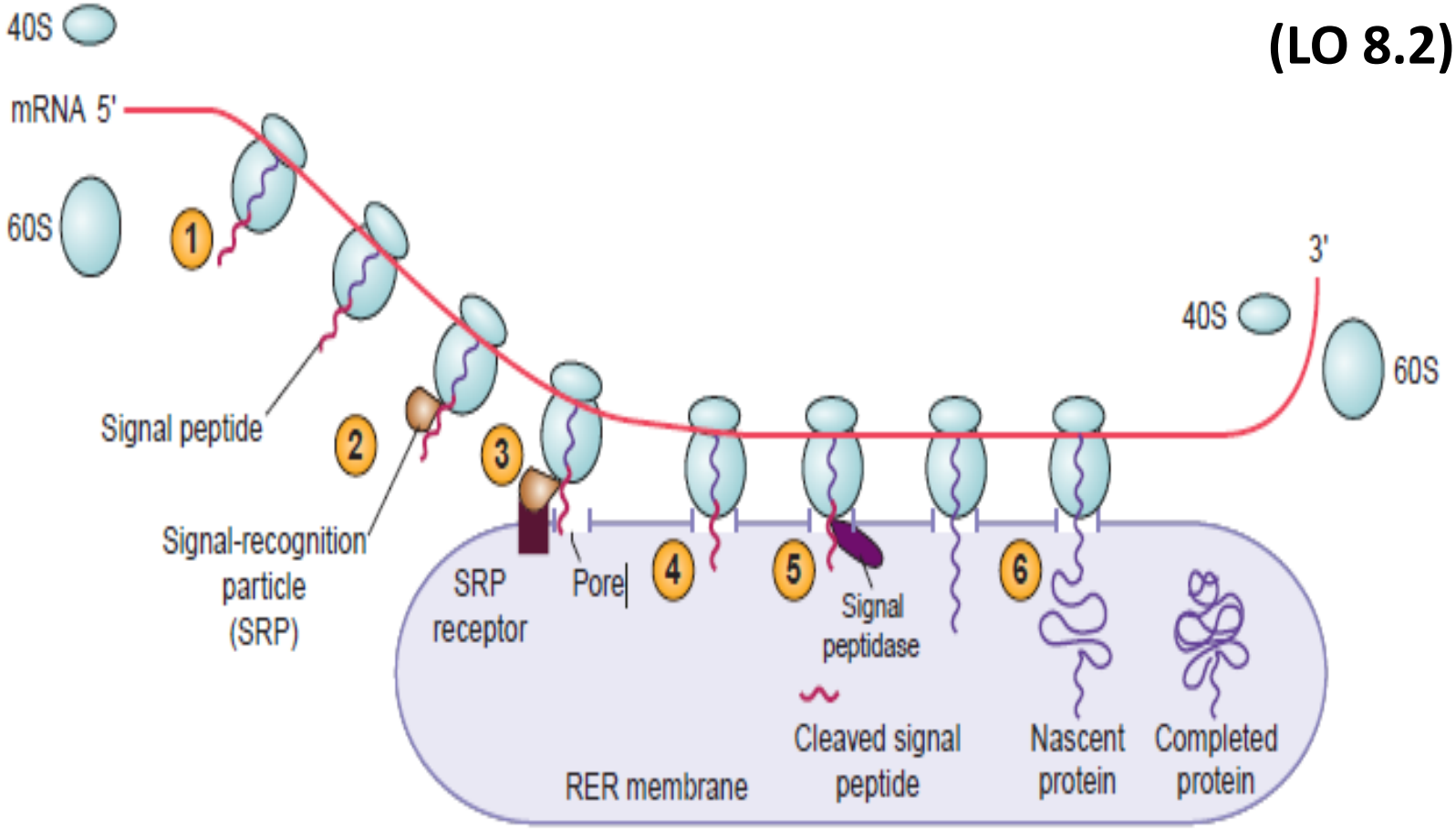


FIG. 15.13. Synthesis of proteins on the RER. *(1)* Translation of the protein begins in the cytosol. *(2)* As the signal peptide emerges from the ribosome, an SRP binds to it and to the ribosome and inhibits further synthesis of the protein. *(3)* The SRP binds to the SRP receptor in the RER membrane, docking the ribosome on the RER. *(4)* The SRP is released and protein synthesis resumes. *(5)* As the signal peptide moves through a pore into the RER, a signal peptidase removes the signal peptide. *(6)* Synthesis of the nascent protein continues, and the completed protein is released into the lumen of the RER.

Ref. (*Marks' Basic Medical Biochemistry* Chapter 15, Page 259)

Protein modifications which occur in the ER and Golgi complex (LO 8.3)

In the ER:

N-linked glycosylation.

- **Removal** of the **signal sequence** by the action of proteases, upon entry of the signal sequence into the lumen of the ER.

In the Golgi:

O-linked glycosylation.

- **Sulfation**: addition of sulfur.
- **Phosphorylation**: addition of phosphate.
- **Proteolysis**: cleavage of peptide bonds.

Distinguish between N-linked and O-linked glycosylation of proteins. (LO 8.4)

Glycosylation: the attachment of carbohydrate groups to proteins via glycosidic linkages.

N-linked glycosylation:

- Occurs in ER.
- Carbohydrate added at the amide group of **asparagine** that is found in a sequence Asn- X-Ser or Asn-X- Thr.

O-linked glycosylation:

- Occurs mainly in Golgi.
- Carbohydrate added to OH group of **serine** or **threonine** amino acids within Asn-X- Ser/Thr sequences.

The role that proteolytic processing plays in the formation of important secreted proteins. (LO 8.5)

For some secretory proteins e.g., growth hormone, removal of the N-terminal signal sequence from the nascent chain is the **only** known proteolytic cleavage required to convert the polypeptide to the mature, active species

(LO 8.5)

However, some plasma-membrane and most secretory proteins initially are synthesized as relatively long-lived, inactive precursors, termed ***proproteins***, which require further proteolytic processing to generate the mature, active proteins.

Examples of proteins that undergo such processing are serum albumin, insulin and glucagon, all of which are secretory proteins.

(LO 8.5)

In **general**, the proteolytic conversion of a **proprotein** to the corresponding mature protein occurs in secretory vesicles as they move away from the trans-Golgi.

Some proproteins, including **proalbumin**, are cut once at a site C-terminal to a dibasic recognition sequence such as Arg-Arg or Lys-Arg.

In other proproteins, additional amino acids are cleaved at the N-terminus or at both ends of the proproteins e.g. proinsulin.

Self-learning:

Targeting of proteins to subcellular & extracellular locations

Ref. (Marks' Basic Medical Biochemistry Chapter 15, Page 259-260)


Thank
you!!!