Protein Targeting

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Competencies as per MCI-CBME Curriculum

- BI 9.3 Explain targeting and sorting along with its associated disorder

Specific Learning Objectives

- Define routine sorting and mechanism involved in targeting of proteins to different organelle.
- Define signal sequence and enlist various signal sequences meant for various organelles.
- Describe the pathways of potein import into mitochondria, nuclei, peroxisome and Endoplasmic Reticulum
- Explain the biochemical mechanism of I-cell disease.
- Discuss the protein targeting defect in Zellweger syndrome.

- Proteins which are synthesized on ‘ polyribosome’ are destined to either various organelles, cytosol, cell membrane or are being exported out.
- Blobel in 1970 proposed that protein need signal or coding sequence to target them appropriately.

Signal Hypothesis

- Proposed by Blobel and Sabatini in 1971.
- In this model, they proposed that membrane bound polyribosomes and cytosolic free polyribosomes have same structure.
- The difference in them is that the former synthesizes a protein which has N- terminal signal peptide , which is responsible for attachment of such polyribosome to the membrane of endoplasmic reticulum (membrane bound polyribosomes) and also allows such proteins to get into the lumen of ER.

Sorting of protein synthesized on rough endoplasmic reticulum

- Proteins synthesized on rough endoplasmic reticulum are destined either for various membranes (membranes of endoplsmic reticulum , golgi apparatus and plasma membrane), lysosome or they may be even secretory protein which are secreted outside the cell.
- Proteins synthesized on rough endoplasmic reticulum have N- terminal signal peptide.
- This signal peptide has approximately 12-35 hydrophobic amino acids rich hydrophobic core and methionine towards N terminal.

- Entry of protein in ER lumen may be a cotranslational or post- translational process.
- This process contains following steps:-

1. N terminal 70 amino acid chain is recognized by **signal recognition particle(SRP),** which contains an RNA molecule in addition to protein components.
2. **SRP-ribosome –protein complex** traverses through endoplasmic reticulum membrane via SRP receptor and translocons.

Role of Golgi apparatus in protein synthesis

A. Golgi apparatus is involved in “O” glycosylation of proteins.

B. Involved in processing of oligosaccharide chain of membrane and other N- linked glycoproteins.

C. Golgi apparatus is involved in sorting of various proteins prior to their delivery to their targets.

- Endoplasmic reticulum contains rich number of chaperons and folding enzymes which assist in protein folding.
- Chaperons and enzymes present in ER are-
  - Calnexin (ER membrane)
  - Calreticulin (ER lumen)
  - BiP(immunoglobulin heavy chain binding protein)
  - GRP94(glucose regulatory protein)
  - PDI (protein disulphide isomerase)

Peptidyl prolyl Cis-trans Isomerase(PPI)

- Misfolded and incompletely folded proteins are retained in endoplasmic reticulum lumen and are prevented from reaching their final destination.
- Change in endoplasmic reticulum Ca2+ status ,redox status, exposure to various toxins and viruses, disturb the internal milieu of the ER lumen leading to accumulation of misfolded proteins.
- Accumulation of such misfolded proteins in ER lumen is known as a state of “ER stress”.

Diseases and affected proteins

Diseases	Affected proteins
Tay –Sachs disease	Beta - hexosaminidase
Gaucher disease	Beta – glucosidase
Cystic fibrosis	CFTR
I cell disease (inclusion cell disease)	N- acetyl glucosamine-1 phosphotransferase
Von willebrand disease	Von willebrand factor
Hemophilia A and B	Factors VIII and IX
Familial hypercholesterolemia	LDL receptor
α1 antitrypsin deficiency with liver disease	α1 antitrypsin
Hereditary hemochromatosis	HFE

PROTEIN DEGRADATION IN EUKARYOTES

- Lysosomal degradation
- Endoplasmic reticulum – associated degradation (ERAD)/ubiquitin – mediated degradation.
- Proteasome.

SORTING OF PROTEINS SYNTHESIZED ON FREE RIBOSOMES IN CYTOSOL

- Cytosolic ribosomes (free ribosomes) synthesized proteins which are targeted to either mitochondria, nucleus, peroxisome or are retained in cytosol itself.
- Uptake of protein by various organelles after its synthesis is complete is known as post – translational translocation.

Protein targeting to mitochondria

- Though the proteins are located at various sub locations of mitochondria - outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM) and matrix.
- Proteins destined for mitochondrial matrix have 20-50 amino acids long pre-sequence or leader sequence which is amphipathic in nature.
- Translocation (passage through OMM and IMM) occurs post-translationally.

Protein Targeting to Nucleus

- Number of proteins and other macromolecules are transported between nucleus and cytosol each minute.

They include :-

- Ribosome subunit
- mRNA
- Ribosomal proteins
- Histone proteins
- Various transcription factors.

Protein targeting in Peroxisome

- Metabolism of following biomolecules requires peroxisome.
- Fatty acid
- Plasmalogen
- Cholesterol
- Bile acid
- Purine
- Amino acid
- H_2O_2.

THANK YOU