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Post-translatonal modification.

Addition of group or deletion of parts to make a finished protein.

- What group—

  methyl

  acetyl

  phospho

- What purpose ----

  targeting(some lipoprotein)

  stability (secreted glycoprotein)

  function (surface glycoprotein).

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Post-translational modification of individual Aminoacids.

- *PHOSPHORYLATION-*

  Phosphorylation of serine , threonine and tyrosine residue occurs by specific kinase. This is a common signal transduction mechanism in hormone action and activation/ inactivation of enzyme e.g.- glycogen synthase and phosphorylase.

- *HYDROXYLATION–-*

  proline and lysine in collagen undergo hydroxylation to form hydroxoproline and hydroxylysine which are again important in the maturation of collagen .

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Modification of Amino acids.

- CARBOXYLATION-

  Carboxylation of glutamate residues in coagulation factor like prothrombin is necessary for their function.

- GLYCOSYLATION-

  Glycosylation occurs by addition of oligosaccharide chains to specific amino acid residue of the polypeptide and is seen in glycoproteins.

- Attachment of gluose to hemoglobin in HBA1c is also an example.

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N AND C TERMINAL MODIFICATION.

- Both formylmethionine and methionine are removed by aminopeptidases. They are not present in most mature proteins.
- Large majority of eukaryotic proteins are acetylated at the N terminal residues.
- C terminal amino acids are also modified in many proteins.

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CLEAVAGE OF NASCENT POLPEPTIDE CHAIN

- Usually the nascent proteins are larger protein than their mature functional counterparts.
- They are called pre-pro-proteins and undergo cleavages
- to become smaller and act

For examples, insulin is synthesized as a much larger-pre-pro-insulin of molecular weight 11500Da while the mature functional insulin is about half the size.

In all 38 amino acids are removed to generate a mature functional insulin molecule

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- Similarly, chymotrypsinogen and trypsinogen are also converted into active chymotrypsin and trypsin by
- cleavage.

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- TRIMMING-
- Many proteins are originally synthesised as much bigger molecules. They undergo proteolytic degradation or trimming to become smaller molecules which are functional Example- the formation of insulin from preproinsulin, conversion of *zymogens* to active digestive enzymes, e.g. trypsinogen to trypsin, pepsinogen to pepsin.

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PROTEIN FOLDING.

- Unique structure of protein involves the folding of its polypeptide chain in a characteristics three dimensional structure.
- This folding is essential for the biological function of the protein.

- CHAPERONS---
- Proteins require other accessory protein called chaperons to promote folding.
- Chaperones are the proteins which interact with partially folded or improperly folded nascent protein to fascilitate correct folding.
- Function—
- 1.Helps in protein folding.
- 2.Prevent Aggregation.
- Ex. Hsp in eukaryotes.

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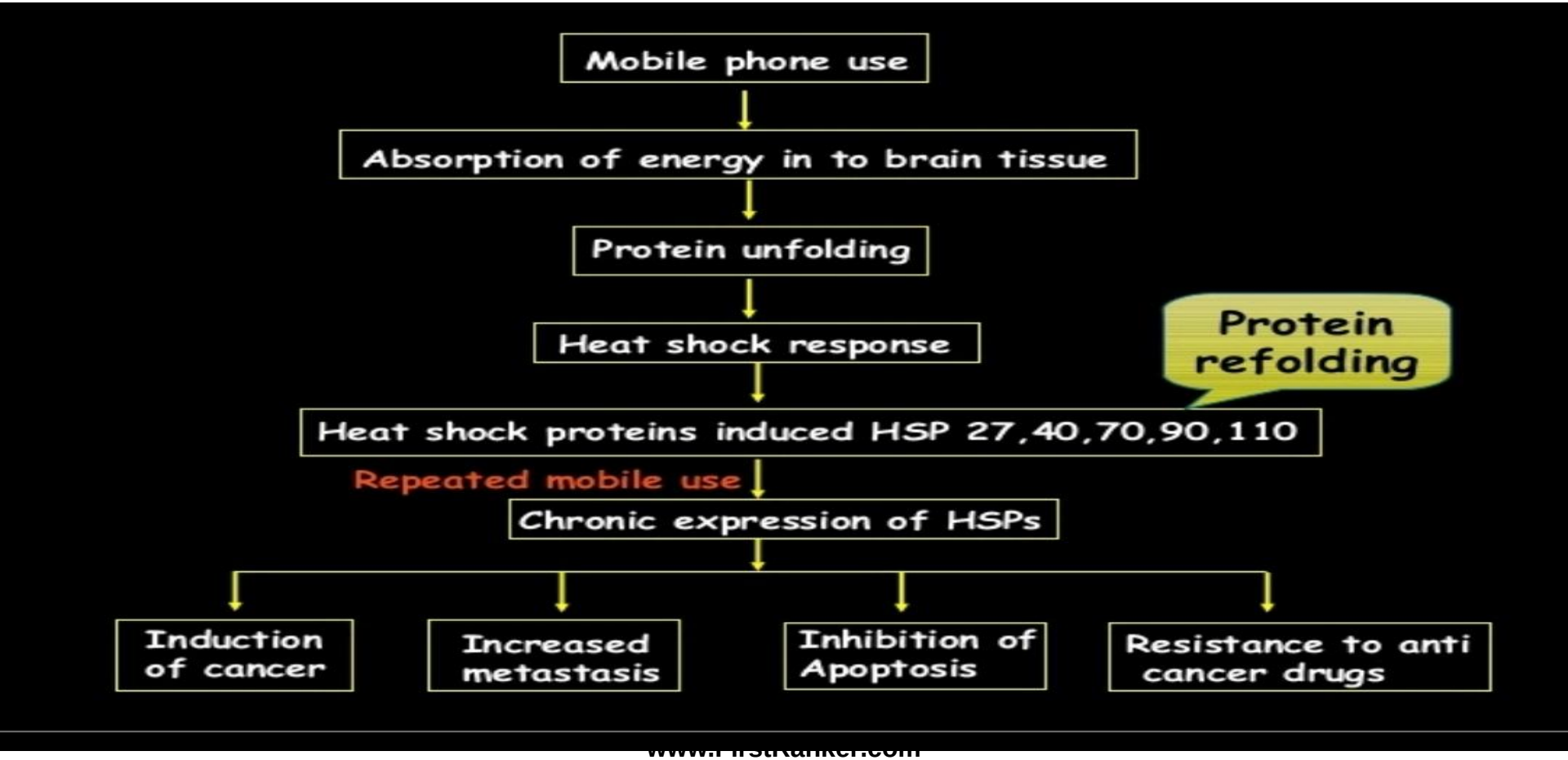
Protein Folding

- Proper folding of protein is essential for a cell to carry outs its normal cellular function.
- Misfolded protein can result in a wide variety of a pathological condition.



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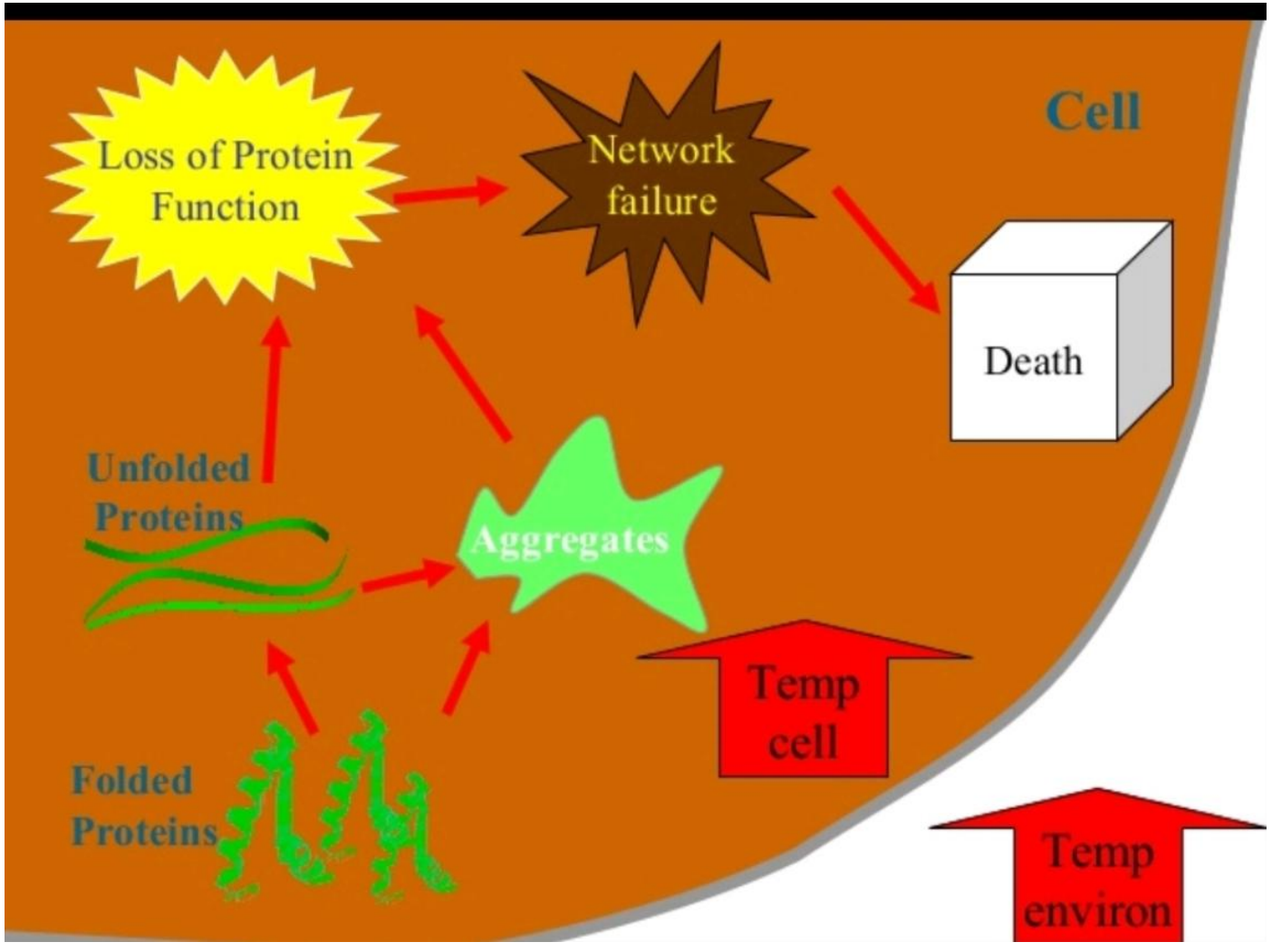
Loss of Protein Function.



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PROTEIN FOLDING.

- These are two classes–
- Hsp70 protein and chaperonins.
- ***Hsp70—***
- The Hsp70 are called heat shock proteins (molecular weight 70KDa) because they are more abundant in cells stressed by heat.
- They are found in all organisms from bacteria to human beings.
- These chaperones protect ptoteins which are denatured by heat and from aggregates.

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- *Chaperonins--*
- The Hsp60 family of proteins are referred to as chaperonins.

- Chaperonins usually act later along with Hsp70.

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PROTEIN MISFOLDING DISEASES.

- Protein misfolding disease can be classified in to two categories.
- Diseases caused due to the misfolding or degradation of misfolded protein.
- Disease caused due to accumulation of misfolded protein.
- ***Reason for protein misfolding---***
- ***Mutation.***
- ***Premature termination of translation.***
- ***Fault in post- translational modification.***

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DISEASE CAUSED DUE TO THE ACCUMULATION OF MISFOLDED PROTEIN.

- **PRION DISEASES—**

- The prion diseases are neuro-degenerative caused by misfolded protein.

- They are characterised by dementia, loss of coordination and encephalitis leading to fatal outcome.

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Prion diseases.

Prion diseases

- Human - Kuru & CJD
- Sheep - Scrapie.
- Cow - Mad Cow disease

Kuru Victim

Mad Cow

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Diseases Due to misfolded protein.

DISEASE	PROTEIN INVOLVED.
Alzheimer's disease	Amyloid Beta – peptide.
Spongiform encephalopaties.	Prion protein
Huntington disease	Huntington protein.

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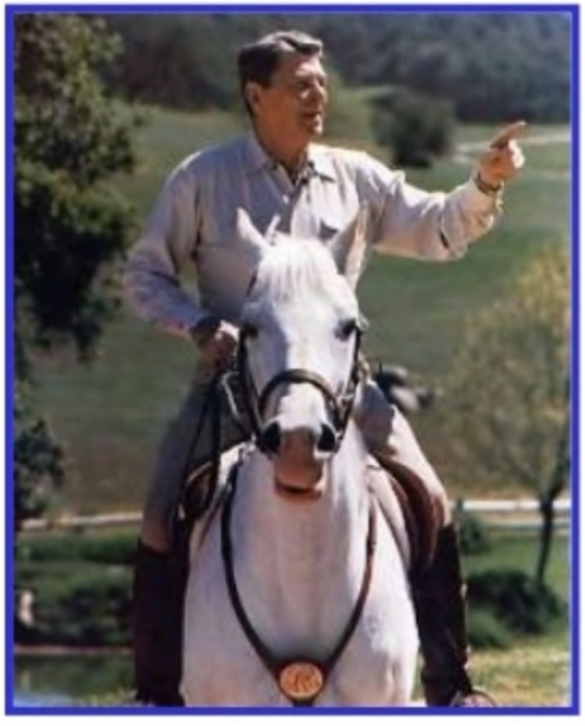
Alzheimer's Disease.



Alzheimer's Disease

"I Have Completely Forgotten Why I came Upstairs "

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Spongiform encephalitis.

- These diseases are also called spongiform encephalitis because they produce vacuolar or spongiform changes in brain.

- The best known examples is mad-cow disease or bovine spongiform encephalitis.

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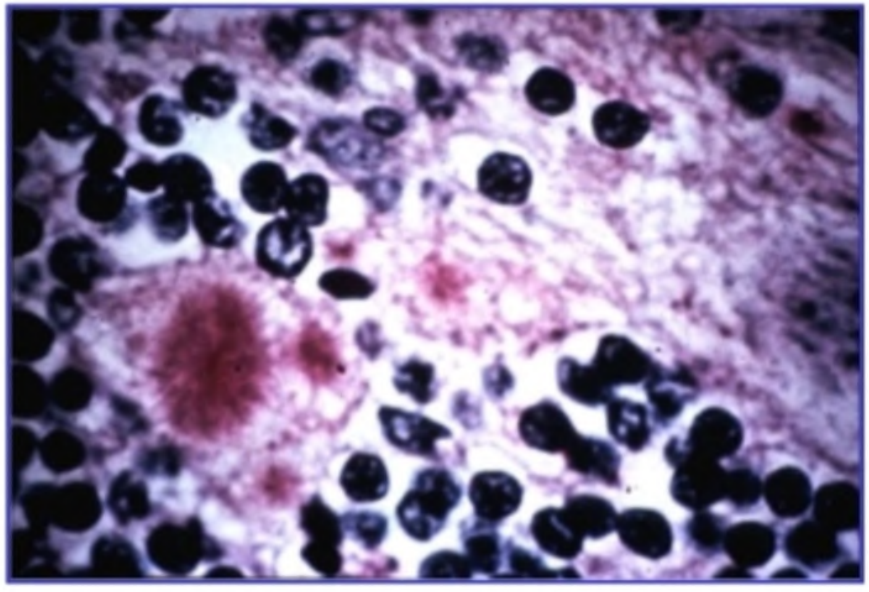
Prion infected Brain of a cattle.

Prion infected Brain of a cattle



Bovine Spongiform Encephalopathy

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Prion disease.

- Creutzfeldt disease is an examples in humans.
- The causative agent is a prion protein---PrP, (moleculer weight 28 Kda) coded by PrP gene on chromosome 20.
- Prion diseases may manifest as genetic, infectious and sporadic diseases.

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PROTEIN TARGETING.

- PROTEIN TARGETING-
- *PROTEIN FOR EXTERNAL SECRETION*
- The process is also called as "protein sorting" or "protein localization". The secreted proteins, plasma membrane integral proteins, lysosomal enzymes and membrane proteins of ER are synthesized on rough **endoplasmic reticulum** by membrane bound polyribosomes. The newly synthesized protein is then delivered to the destined compartment. Blobel and sabatini proposed the **signal hypothesis** to explain the different destination of proteins. Guenter Blobel was awarded Nobel Price in 1999.

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Protein targeting.

- Protein targeting or protein sorting is the mechanism by which a cell transport to the appropriate positions in the cell or outside of it.
- Protein targeting is necessory for protein that are destined to work outside the cytoplasm.
- The delivery process is carried out based on information contained in the protein itself.
- Correct sorting is crucial for the cell, errors can lead to disease.
- Synthesized protein is transferred to an SRP receptor on endoplasmic reticulum, nascent protein is inserted into translocation complex.

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Targeting signal.

- Targeting signal are the piece of information that enable the cellular transport machinery to correctly position a protein inside or outside the cell.
- This information is contained in the polypeptide chain or in the folded protein.
- In abscence of targeting signal, a protein will remain in the cytoplasm.

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Protein targeting.

- Protein has to correctly localised to perform proper function.
- Receptor---plasma membrane.
- DNA polymerase—nucleus.
- Catalase-----peroxisomes.
- Insulin-------outside.

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- All protein begins to be synthesized on cytosolic ribosomes.
- Sorting or translocation can occur
- Co- tranlational.
- Post-translational.
- If protein is for cytosolic function, the synthesis will be finished on free ribosomes and the peptide is released into the cytosol.

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Protein targeting.

- The nascent protein is passed through the membrane into the channels of ER. Then protein synthesis is completed, and the protein molecule is now inside the endoplasmic membrane. As the nascent protein is traversing the inner membrane of ER, carbohydrate moieties are added at particular regions by specific enzymes; this is called co-translational glycosylation.

- CORRECT ADDRESS of DESTINATION is LABELED

  The protiens carry an "address" that is specific for its correct destination inside the cell. This is present in the **carboxy terminal** end of proteins. Diseases due to defective protein targeting.

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Protein targeting.

Protein Targeting

Zellweger syndrome is due to defective oxidation of very long chain fatty acids (VLCFA). Here the correct "address" is not printed on the protein packet; so that it could not be delivered to the correct location. Peroxisomal enzymes are produced; but their entry into peroxisomal is denied. This leads to insufficient oxidation of VLCFA. Accumulation of VLCFA in CNS causes neurological impairment and death in childhood.

Another example is primary hyperoxaluria, which causes kidney stones at an early age. The defect is due to protein trageting defect and the enzyme alanine glyoxylate amino transferase seen in mitochondria, instead of its normal peroxisomal location.

lysosomes cell diseases due to non-entry of normal enzymes into lysosomes. Mannose-6-phosphate is the marker to target enzymes to lysosomes;this is absent.

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MITOCHONDRIAL DNA and RNA.

- Some of mitochondrial protein synthesis is under the control of mitochondrial DNA;
- but important proteins of the outer membrane of the mitochondria are synthesized under the influence of nuclear DNA.
- Shows that mitochondria are similar to bacteria more than mammalian cells.
- This fact supports the theory that mitochondria are derived from prokaryotes symbiotically adapted to multicellular organisms.

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- **Maternal inheritance:**

- Since, the mitochondria are inherited cytoplasmically, the mtDNA is inherited from the mother.

- Mother transmits mtDNA through oocyte.

- There are hunderds of copies of mtDNA in each cell (nuclear DNA has only 2 copies).

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- During cell division, mtDNA replicates and they segregate to the daughter cells.
- If a mutation occurs in mtDNA, the daughter cells may inherit the mutant or normal mtDNA.
- **Heteroplasmy** is defined as the presence of normal and mutant mtDNA in different proportions in different cells.

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Defects in mitochondrial genome will lead to mitochondrial **myopathies**.

- Leber`s hereditary optic neuropathy is caused by a single base mutation which alters one argrinine to histidine in the NADH Coenzyme Q reductase. OXPHOS (oxidative phosphorylation).

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OXPHOS DISEASES

Syndrome	*Features*
Leber`s Hereditary Neuropathy(LHON)	Complex I defect; blindness,cardiac conduction defects
Myoclonic epilepsy ragged Red fiber diseases (MERRF)	Myoclonic epilepsy, myopathy, dementia
Leigh`s syndrome	Complex I defect ; movement disorders

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GENOME AND PROTEOME.

- All the DNA contained in an organism or a cell which includes both the chrosomes within the nucleus and the DNA in mitochondria----GENOME.

- PROTEOME—Is the some of all proteins expressed by the genome of an organism.

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