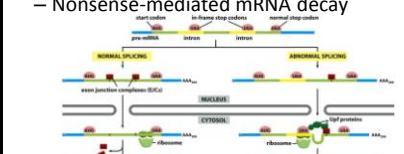


Chapter 6

How Cells Read the Genome

Quality Control Mechanisms Act to Prevent Translation of Damaged mRNAs

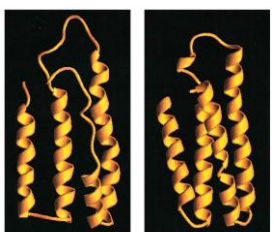
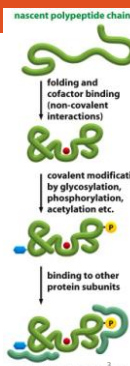
- Eukaryotes
 - Transcription → RNA-processing → Transport → Translation
 - Incorrect processing, damage in cytoplasm
- Backup measures
 - 5' cap & poly-A tail & Exon junction complex
 - Nonsense-mediated mRNA decay



Some Proteins Begin to Fold While Still Being Synthesized

nascent polypeptide chain

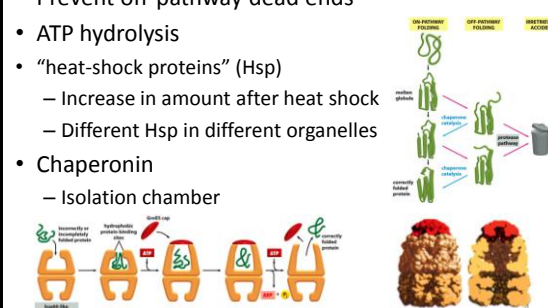
- Molten globule
 - Cytochrome b562
 - side chain adjustments

mature functional protein

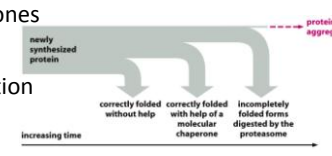
Molecular Chaperones Help Guide the Folding of Most Proteins

- Prevent off-pathway dead ends
- ATP hydrolysis
- “heat-shock proteins” (Hsp)
 - Increase in amount after heat shock
 - Different Hsp in different organelles
- Chaperonin
 - Isolation chamber



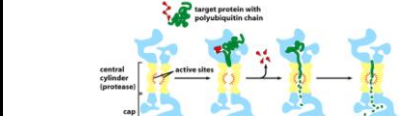
Exposed Hydrophobic Regions Provide Critical Signals for Protein Quality Control

- Exposed hydrophobic regions
 - Abnormal folding
 - Accident
 - Failure to bind to partner subunit
- Signal to chaperones
- Prevent aggregation
 - Toxic affects



The Proteasome Is a Compartmentalized Protease with Sequestered Active Sites

- Constant competition with chaperones
 - Slow folding is more venerable to proteasome
 - 1% of cellular protein
 - ATP-dependent
 - Signaled by ubiquitin tags
 - # and linkage determines interpretation of tags




An Elaborate Ubiquitin-Conjugating System Marks Proteins for Destruction

- Action taken by cell depends on specific ubiquitin patterns


MONO-UBIQUITYLATION

MULTI-UBIQUITYLATION


POLYUBIQUITYLATION




histone regulation



endocytosis



proteasomal degradation



DNA repair

Many Proteins Are Controlled by Regulated Destruction

- Maintain specific protein lifetimes
 - Constant
 - Conditional
 - Intracellular or environmental
 - Ubiquitylation & destruction
- Creation of degradation signal
 - Phosphorylate specific site
 - Dissociation of subunit
 - Single peptide bond cleavage
 - 12 destabilizing N terminal residues
 - R, K, H, F, L, Y, W, I, D, E, N, Q

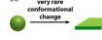
Abnormally Folded Proteins Can Aggregate to Cause Destructive Human Diseases

- Escape controls → abnormally fold → form aggregates
- Damage or kill cells
- Can be age related
 - Decline of cells protein quality controls
- Aggregates released from dead cells accumulate
 - Damage tissue
 - Nerve cells vulnerable
 - Neurodegenerative diseases
 - Huntington's, Alzheimer's

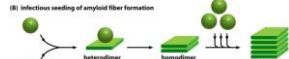
Proteolysis resistant proteins


- Fibrils
 - Continuous β -sheet stacks
 - Cause amyloid deposits
- Prions
 - Misfolded PrP (prion protein)
 - Scrapie – sheep
 - Creutzfeldt-Jacob disease – human
 - Bovine spongiform encephalopathy-cattle

(A) very rare conformational change



(B) infectious seeding of amyloid fiber formation

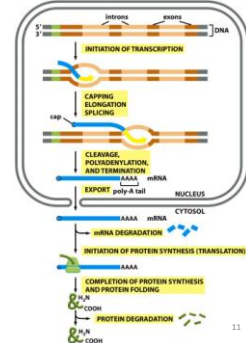


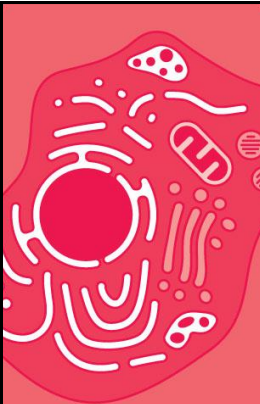


5 nm

There Are Many Steps From DNA to Protein

- Protein levels
 - Depend on efficiency of each step





Chapter 12

Intracellular Compartments and Protein Sorting

