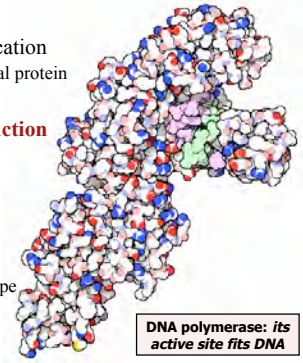
Protein Shape Determines Function

- Post-translation modification
  - polypeptide functional protein
- Specific 3-D shape
- **Shape is critical to function**

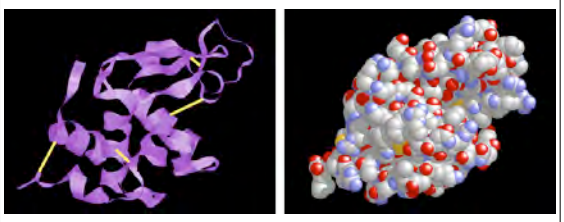
- **Denaturation** = loss of shape
  ➨ loss of function



DNA polymerase: *its active site fits DNA*

Protein Structure

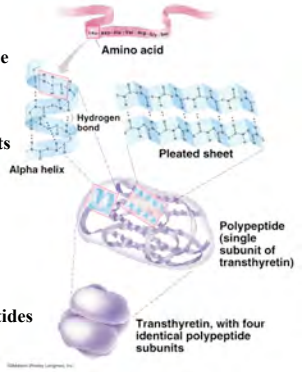
A protein's specific function depends on its shape and distribution of functional groups.



lysozyme

Levels of Protein Structure

- **Primary**
  - **Polypeptide sequence**
- **Secondary**
  - **Folding coils & pleats**
- **Tertiary**
  - **Complete 3-D shape**
- **Quarternary**
  - **Combining polypeptides**



Primary structure of protein: the amino acid sequence

Primary structure is due to strong covalent peptide bonds joining amino acids together.

lysozyme

Primary Structure & Protein Trafficking

Leading sequence of amino acids in a polypeptide being synthesized determines its fate: cytosolic, membrane-bound, nuclear, or secreted.

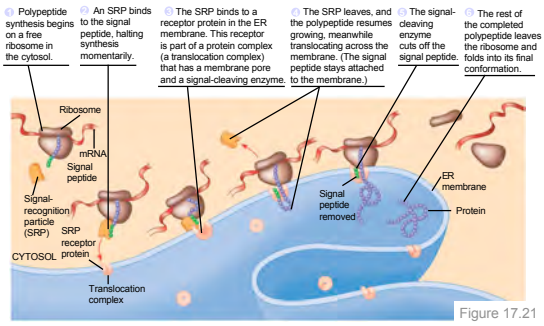


Figure 17.21

Modification of primary structure

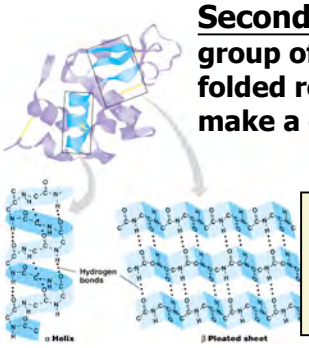
- Chemical alteration of amino acid side groups
  - Methylation; hydroxylation; etc.
  - E.g.:
    - N-terminal methyl-methionine protects peptide from amino-peptidases.
    - Collagen contains many hydroxy-prolines & hydroxy-lysines allows condensation with oligosaccharides

Modification of primary structure

- Cleavage of polypeptide chain
  - Zymogens:
    - inactive pre-enzyme minus fragment active enzyme
  - Isolation of fragments within a protein:
    - Insulin polypeptide folds over to be cross-linked with itself, and is then cleaved into two polypeptides
  - Multiple products:
    - **P**ro-**o**pio**m**elano**c**ortin (POMC) — translated polypeptide cleaved into fragments:
      1. Endorphin (opioid)
      2. Melanocyte stimulating hormone
      3. Corticotropin stimulating hormone

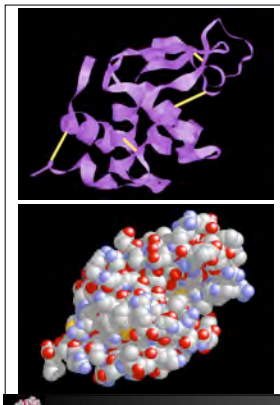
Secondary structure:

group of amino acids folded repetitively to make a discrete shape.



due to hydrogen bonds between amino acids' backbones.

Tertiary structure:



the overall 3-d conformation of a polypeptide.

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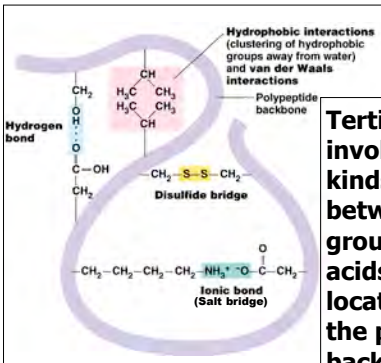
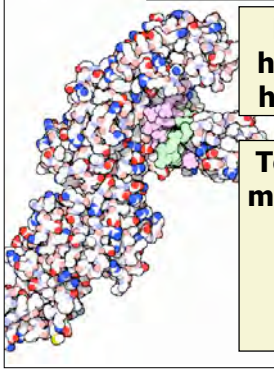


Tertiary structure involves several kinds of bonds between side groups of amino acids at various locations along the polypeptide backbone.

Covalent disulfide bonds between cystine residues are the strongest and most stable.

Tertiary Structure



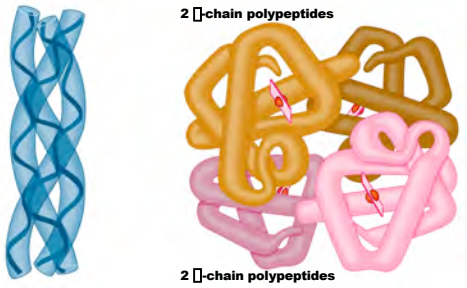
Most proteins are hydrophilic outside, hydrophobic inside.

Tertiary structure is maintained by amino acids interacting with other amino acids and with water.

Quaternary Structure

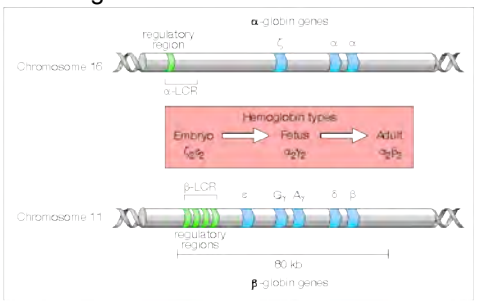
Multiple polypeptides joined to make a single protein. (May be the same or products of separate genes)

Quaternary Structure



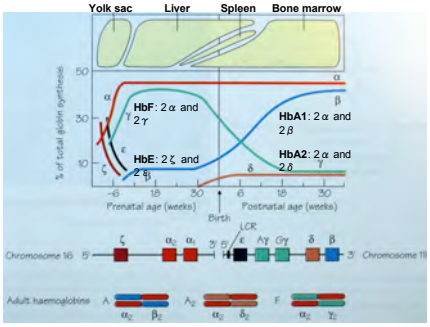
collagen ***hemoglobin***

Hemoglobin Genes and Gene Products



http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch09/fig9_24.jpg

Hemoglobin Gene Product Production



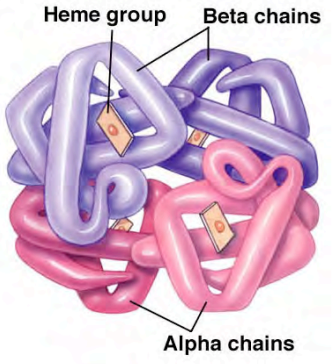
Mehta, A. B., and A. V. Hoffbrand. 2000. Haematology at a glance, Blackwell Science, Malden, Mass.

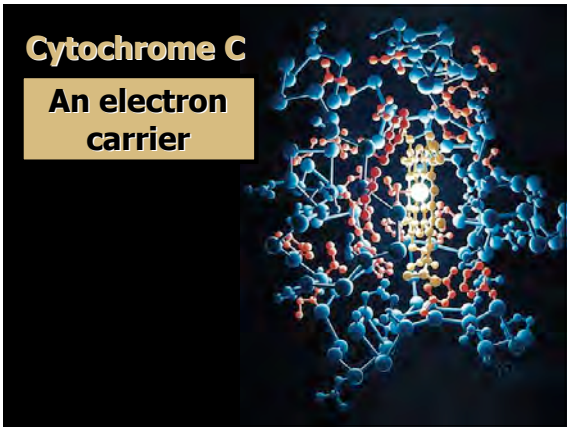
Prosthetic groups

Non-amino acid groups added to a polypeptide.

- Carbohydrate glycoprotein
- Lipid lipoprotein
- Nucleic acid nucleoprotein
- Phosphate phosphoprotein
  - "activated" protein
- Metal ion metalloprotein
- Heme (organic porphyrin ring with an iron core) hemoprotein

Hemoglobin Molecule





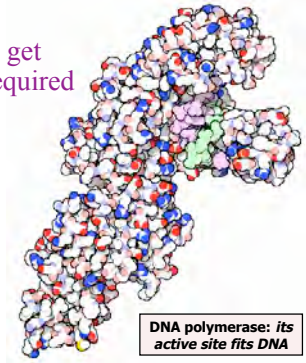
How Proteins Fold

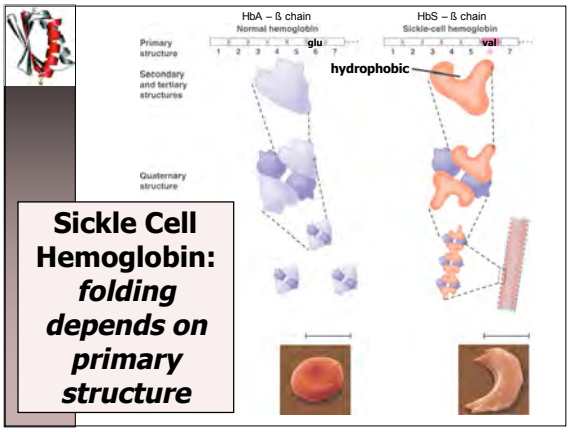
- **A protein's function depends on its folding.**

DNA polymerase: *its active site fits DNA*

Protein Shape Determines Function

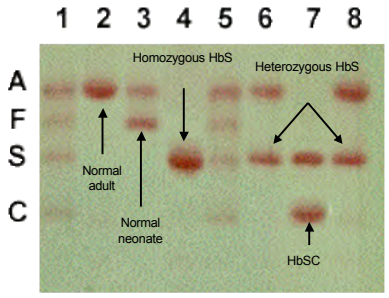
- **How** do proteins get folded into the required conformation?





Sickle Cell Hemoglobin: *folding depends on primary structure*

Hemoglobin Electrophoresis

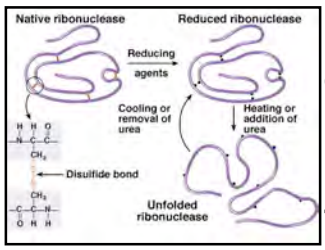


http://themedicalbiochemistrypage.org/hemoglobin-myoglobin.html

How Proteins Fold

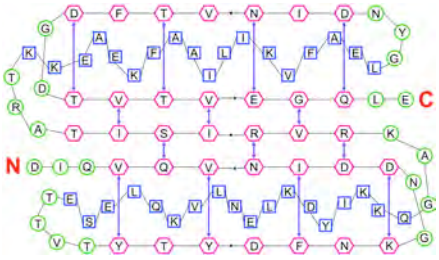
- **A protein's function depends on its folding.**
- **There may be more than 1 way for a big polypeptide to fold.**

Protein folding: Is it all downhill?



Ribonuclease can renature itself. This makes it an unusually tough protein.

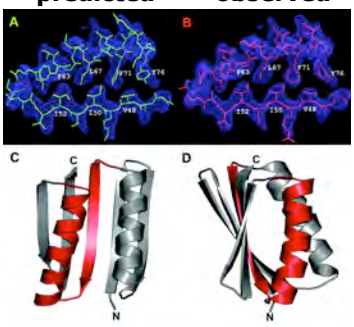
Designing a protein to fold



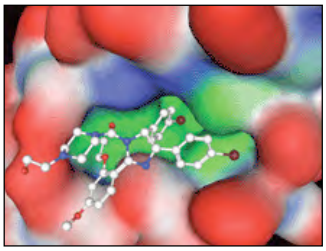
⬡ —hydrophobic amino acid residues

Structure of an artificial protein

predicted observed



Understanding protein structure is important



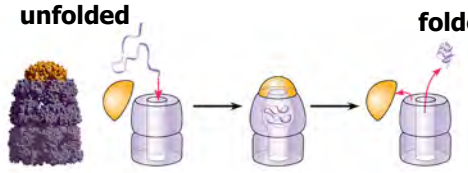
Nutlin, a tumor-suppressing drug that mimics the shape of protein p53 (transcription factor).

How Proteins Fold

- A protein's function depends on its folding.
- There may be more than 1 way for a big polypeptide to fold.
- **Some proteins can fold on their own, but many require help.**
- **Chaperonins are proteins that help fold other proteins.**

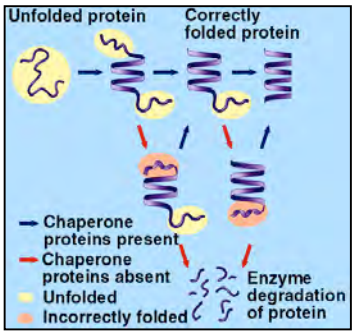
A Chaperonin

unfolded folded



Provides a "safe folding environment"

— Probably binds to polypeptide, to induce the correct folding conformation



Unfolded or incompletely folded proteins may be destroyed.

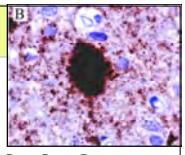
Proteins
the Molecular Machines

- Incorrectly folded proteins don't work, and they clump together (they become insoluble).
- If not refolded or destroyed, they can accumulate and cause problems.
  - Eg., excess accumulated misfolded proteins (plaques) in neural tissue
    - Parkinson disease
    - Alzheimers disease
    - Mad cow disease

Prions

infectious protein agents

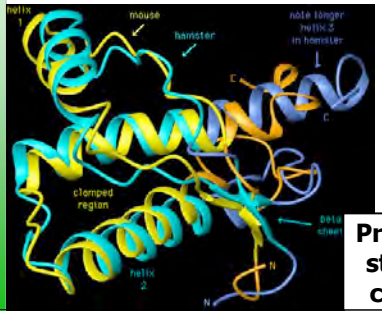
Prion Basics



- Prions are an unusual kind of misfolded protein.
- Prions can cause CNS diseases like mad cow, scrapie, kuru, and Creutzfeldt-Jakob disease.
- Prions can be transmitted from one individual to another.

Prion Basics

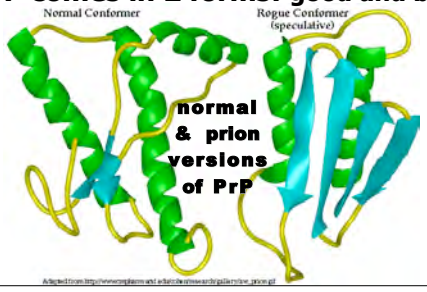
- Everybody has prion proteins (PrP).



Prion protein structure is conserved.

Prion Basics

- Everybody has prion proteins (PrP).
- PrP comes in 2 forms: good and bad.



Prion Basics

- Everybody has prion proteins (PrP).
- PrP comes in 2 forms: good and bad.
- **Bad PrP catalyzes the misfolding of good PrP, changing good PrP to bad.**

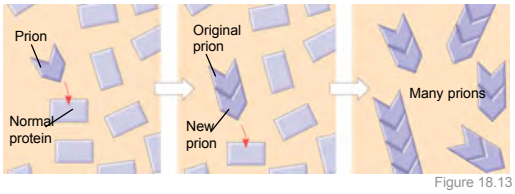
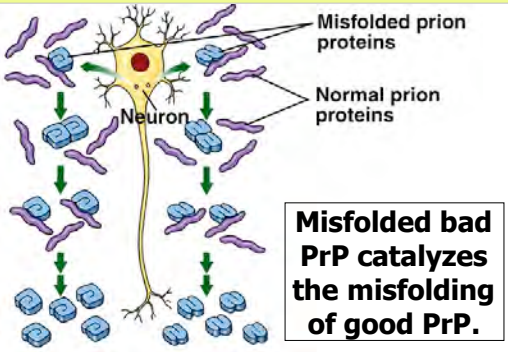


Figure 18.13



Misfolded bad PrP catalyzes the misfolding of good PrP.

Prion Basics

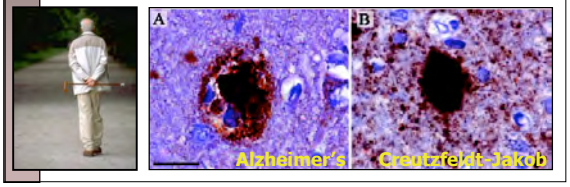
- Everybody has prion proteins (PrP).
- PrP comes in 2 forms: good and bad.
- Bad PrP catalyzes the misfolding of good PrP, changing good PrP to bad.
- **Consuming bad PrP can turn all your good PrP bad (chain reaction).**
  - **Transmitted by food, transfusions, transplants, brain extracts.**

Prion Disease: Open Questions

- **What does good PrP normally do?**
- **How specifically does bad PrP convert good PrP?**
- **Can conversion be blocked?**
- **Why isn't PrP digested/destroyed when eaten?**
- **How does bad PrP get to the brain?**
- **How does bad PrP cause disease?**

Other Protein Folding Research

- **Alzheimer's disease is completely different from prion diseases.**
- **However, both are caused by accumulations of misfolded proteins.**



Accumulations of misfolded proteins

- **Prion disease: misfolded protein catalyzes more misfolding.**
- **Alzheimer's: cause of misfolding unknown, but failure of "unfolded protein response" pathway is key.**