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Learning Outcomes

1. Explain the relationship between proteins and amino acids.
2. Explain the relationship between genes and proteins.
3. List the major types of RNA molecules and their functions.
4. Explain the importance of transcription factors.
5. List the steps of transcription.
6. Discuss how researchers deduced the genetic code.
7. List the steps of protein synthesis.
8. Define the four components of a protein's shape.
9. Explain the importance of protein folding.

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Proteins 1

Dietary proteins are digested into **amino acids**.

Genes control the linking of amino acids into proteins.

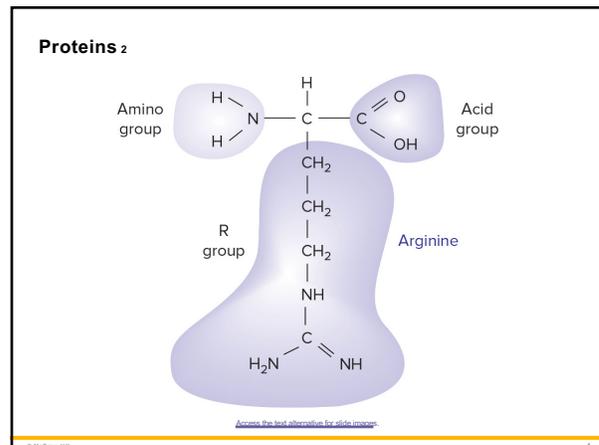
20 amino acids are required for the body to produce its own protein molecules.

- Nine of the 20 are considered essential

Each amino acid has a central carbon atom that bonds to an amino group (NH₂) and an acidic group (COOH), a hydrogen atom (H), and a variable "R" group.

- It is the R group that distinguishes the 20 types of amino acids.

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Proteins 3

- The 20,325 or so proteins the human has are coded by protein coding genes, termed the exome.
- Proteins serve many vital functions; some of these functions are contractile, regulatory, enzymatic, structural, transport, immunity, and clotting.
- Proteins are comprised of one or more long chains of amino acids called **polypeptides**.
- A protein's three-dimensional shape is called its **conformation**

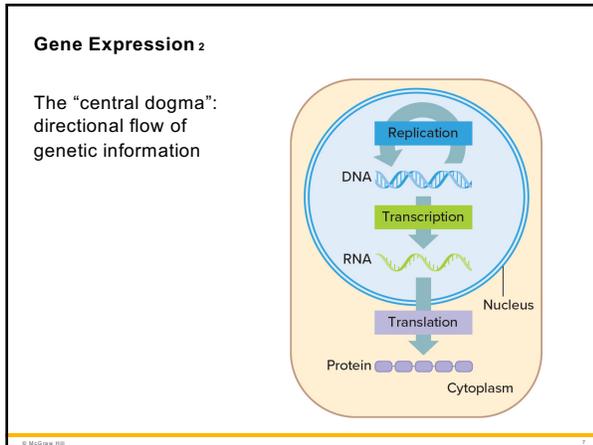
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Gene Expression 1

A cell uses two processes to manufacture proteins using genetic instructions

- **Transcription** = Synthesizes an RNA molecule
- **Translation** = Uses the information in the RNA to manufacture a protein by aligning and joining specified amino acids
- Folding of the protein into specific 3-D form necessary for its function

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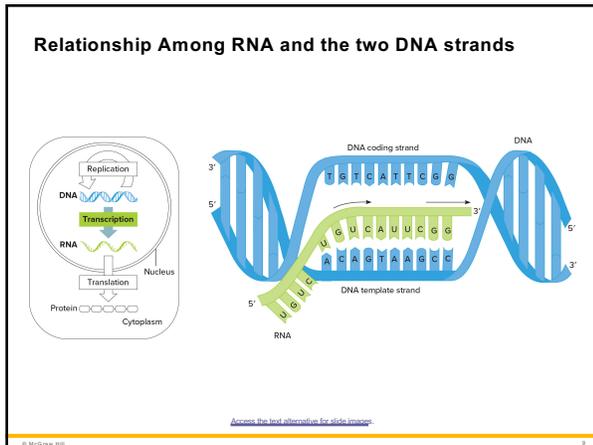
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RNA Structure and Types

- RNA is the bridge between gene and protein.
- Bases of an RNA sequence are complementary to those of one strand of the double helix, called the **template strand**.
- **RNA polymerase** builds an RNA molecule.
- Nontemplate strand of the DNA double helix is called the **coding strand**.

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Nucleic Acids 1

There are two types of nucleic acids:

- RNA
- DNA

Both consist of sequences of nitrogen-containing bases joined by sugar-phosphate backbones.

- However, they differ in several aspects.

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Nucleic Acids 2

Table 10.1 How DNA and RNA Differ

DNA	RNA
1. Usually double-stranded	1. Usually single-stranded
2. Thymine as a base	2. Uracil as a base
3. Deoxyribose as the sugar	3. Ribose as the sugar
4. Maintains protein-encoding information	4. Carries protein-encoding information and controls how information is used
5. Cannot function as an enzyme	5. Can function as an enzyme
6. Persists	6. Short-lived

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DNA and RNA Differences

DNA

- Stores RNA- and protein-encoding information, and transfers information to daughter cells

RNA

- Carries protein-encoding information, and helps to make proteins

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Types of RNA 1

There are three major types of RNA:

- **Messenger RNA or mRNA**
 - Carries the information for a particular protein
- **Ribosomal RNA or rRNA**
 - Associates with certain proteins to form ribosomes
- **Transfer RNA or tRNA**
 - Binds to mRNA at one end and a specific amino acid at the other.

Other classes of RNA control which genes are expressed (transcribed and translated) under specific circumstances

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Types of RNA 2

Table 10.2 Major Types of RNA

Type of RNA	Size (number of nucleotides)	Function
Messenger RNA (mRNA)	500 to 4,500+	Encodes amino acid sequence
Ribosomal RNA (rRNA)	100 to 3,000	Associates with proteins to form ribosomes, which structurally support and catalyze protein synthesis
Transfer RNA (tRNA)	75 to 80	Transports specific amino acids to the ribosome for protein synthesis

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mRNA

Carries information that specifies a particular protein

Three mRNA bases in a row form a **codon** which specifies a particular amino acid

Most mRNAs are 500 to 4,500 bases long

Differentiated cells produce certain mRNA molecules called transcripts

- Information in the transcripts is used to manufacture the encoded proteins

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rRNA 1

Most rRNAs are from 100 to 3,000 nucleotides long

Associate with certain proteins to form ribosomes

Ribosomes consist of two subunits that join during protein synthesis

rRNAs provide more than structural support

- Some are catalysts (**ribozymes**) and others help align the ribosome and mRNA

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rRNA 2

Large subunit

5,347 RNA bases (in 3 molecules)
47 proteins

Small subunit

1,869 RNA bases (in a single molecule)
32 proteins

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tRNA 1

Binds an mRNA codon and a specific amino acid

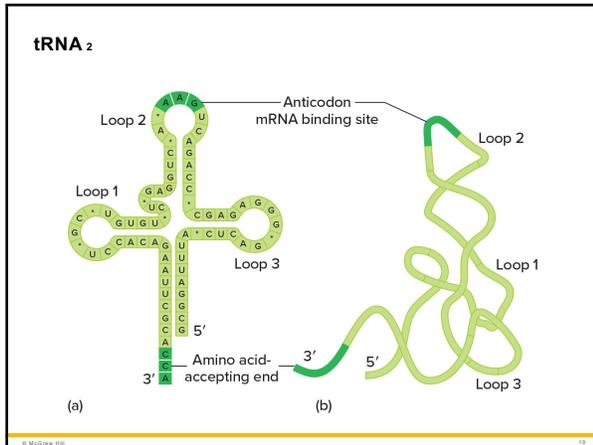
Only 75 to 80 nucleotides long

- The 2-D shape is a cloverleaf shape
- The 3-D shape is an inverted L

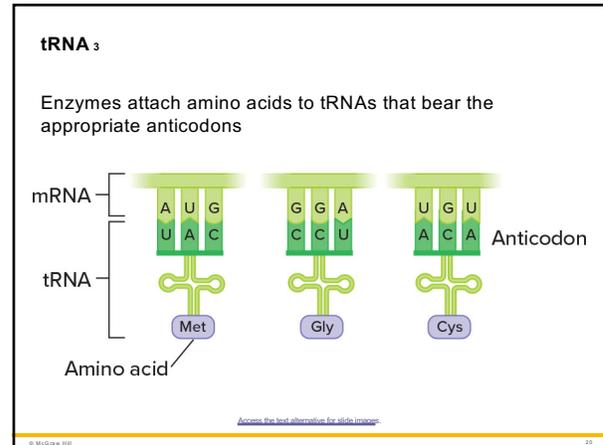
Has two ends:

- The **anticodon** is complementary to an mRNA codon
- The opposite end strongly bonds to a specific amino acid

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Transcription Factors

- Interact and form an apparatus that binds DNA at certain sequences
- Initiate transcription at specific sites on chromosomes
- Respond to signals from outside the cell
- Link the genome to the environment
- Mutations in transcription factors may cause a wide range of effects

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Steps of Transcription 1

Transcription is described in three steps:

- Initiation
- Elongation
- Termination

In transcription initiation, transcription factors and RNA polymerase are attracted to a **promoter**.

RNA polymerase joins the complex, binding in front of the start of the gene sequence.

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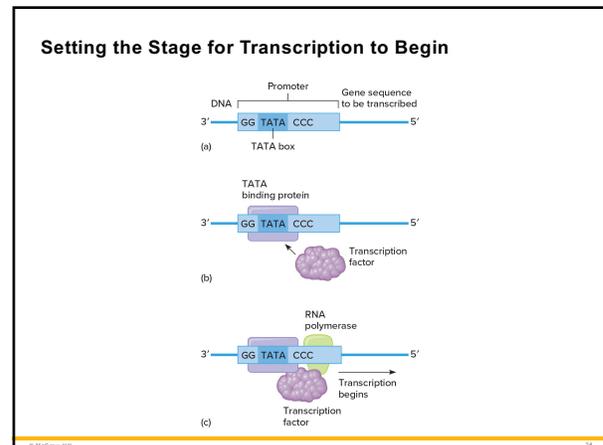
Steps of Transcription 2

In transcription elongation, enzymes unwind the DNA double helix.

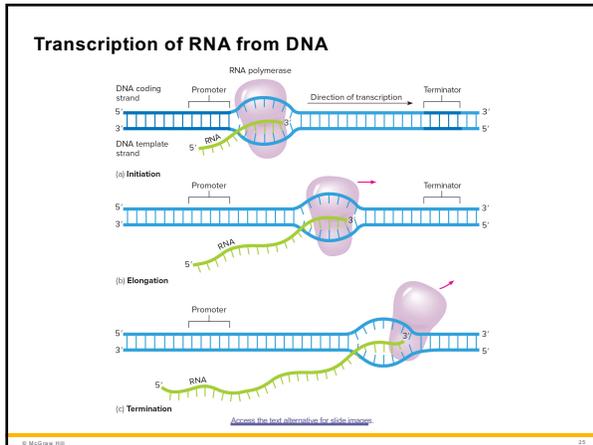
- Free RNA nucleotides bond with exposed complementary bases on the DNA template strand.
- RNA polymerase adds the RNA nucleotides, in the sequence the DNA specifies.

A terminator sequence in the DNA indicates where the gene's RNA-encoding region ends.

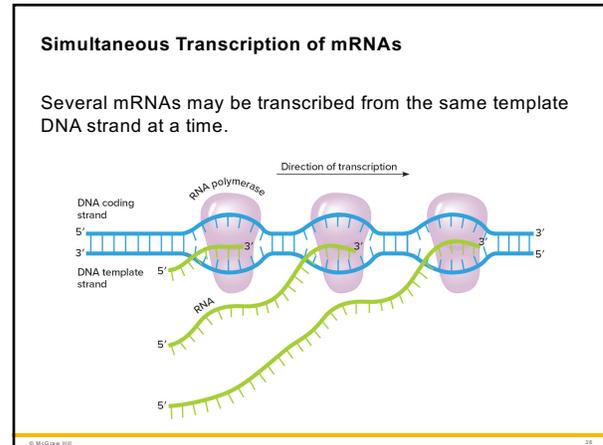
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RNA Processing 1

In eukaryotes, mRNA must exit the nucleus to enter the cytoplasm.

Several steps process pre-mRNA into mature mRNA.

- A methylated cap is added to the 5' end.
 - Recognition site for protein synthesis
- A poly A tail is added to the 3' end.
 - Necessary for protein synthesis to begin and stabilizes the mRNA

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RNA Processing 2

- Splicing occurs.
 - **Introns** ("intervening sequences") are removed.
 - Ends of the remaining molecule are spliced together.
 - **Exons** are parts of mRNA that remain, translated into amino acid sequences.
 - Note that introns may outnumber and outsize exons.
- mRNA is proofread and the mature mRNA is sent out of the nucleus.

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RNA Processing 3

The intron/exon organization of genes maximizes genetic information.

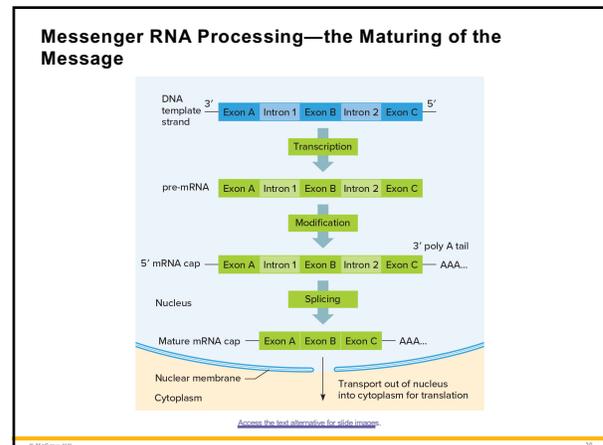
Different combinations of exons of about 95 percent of human genes encode different versions of a protein, termed **isoforms**.

The mechanism of combining exons of a gene in different ways is called **alternative splicing**.

- Cell types can use versions of the same protein in slightly different ways in different tissues

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Translation

Assembles a protein using the information in the mRNA sequence

- Particular mRNA codons correspond to particular amino acids

Occurs on the ribosome

The diagram illustrates the process of translation. It starts with a DNA double helix. The top strand is the DNA template strand with the sequence 3'-TTCAGTCAAG-5'. The bottom strand is the messenger RNA (mRNA) with the sequence 5'-AAGUCAGUC-3'. The mRNA is transcribed from the DNA template. The mRNA is then translated into a polypeptide chain consisting of the amino acids Lysine, Serine, and Valine. The mRNA sequence is divided into three codons: AAG, UCA, and GUC. Arrows indicate the flow from DNA to mRNA (Transcription) and from mRNA to Protein (Translation).

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The Genetic Code 1

- The correspondence between the chemical languages of mRNA and proteins
- In the 1960s, researchers used logic and clever experiments on simple genetic systems to decipher the genetic code

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The Genetic Code 2

Table 10.3 The Genetic Code*

First Letter	Second Letter				Third Letter
	U	C	A	G	
U	UUU } Phenylalanine (Phe)	UCU } Serine (Ser)	UUU } Tyrosine (Tyr)	UUU } Cysteine (Cys)	U
	UUC } Leucine (Leu)		UUC } "stop"	UUC } "stop"	C
	UUA } Leucine (Leu)		UUA } "stop"	UUA } "stop"	A
	UUG } Leucine (Leu)		UUG } "stop"	UUG } Tryptophan (Trp)	G
C	CUU } Leucine (Leu)	CCU } Proline (Pro)	CAU } Histidine (His)	CSU } Arginine (Arg)	U
	CUC } Leucine (Leu)		CAC } Glutamine (Gln)	CUC } Arginine (Arg)	C
	CUA } Leucine (Leu)		CAA } Glutamine (Gln)	CUA } Arginine (Arg)	A
	CUG } Leucine (Leu)		CAG } Glutamine (Gln)	CUG } Arginine (Arg)	G
A	AUU } Isoleucine (Ile)	ACU } Threonine (Thr)	AUU } Asparagine (Asn)	ASU } Serine (Ser)	U
	AUC } Isoleucine (Ile)		AAC } Lysine (Lys)	AUC } Serine (Ser)	C
	AUA } Methionine (Met) and "start"		AUA } Lysine (Lys)	AUA } Arginine (Arg)	A
	AUG } Methionine (Met) and "start"		AAG } Lysine (Lys)	AUG } Arginine (Arg)	G
G	GUU } Valine (Val)	GCU } Alanine (Ala)	GAU } Aspartic acid (Asp)	GSU } Glycine (Gly)	U
	GUC } Valine (Val)		GAC } Aspartic acid (Asp)	GUC } Glycine (Gly)	C
	GUA } Valine (Val)		GAA } Glutamic acid (Glu)	GUA } Glycine (Gly)	A
	GUG } Valine (Val)		GAG } Glutamic acid (Glu)	GUG } Glycine (Gly)	G

*The genetic code consists of mRNA triplets and the amino acids that they specify.

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Characteristics of the Genetic Code 1

It is a triplet code.

- Three successive mRNA bases form a codon.
- There are 64 codons.
- Altering the DNA sequence by one or two bases produced a different amino acid sequence due to disruption in the **reading frame**.
 - Adding a base at one point and deleting a base at another point disrupted the reading frame between the sites.
 - This is termed a **frame-shift mutation**

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Characteristics of the Genetic Code 2

It is nonoverlapping.

- In an overlapping DNA sequence, certain amino acids would follow others, constraining protein structure

It includes controls.

- Includes directions for starting and stopping translation
 - An **open reading frame** does not include a stop codon

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Characteristics of the Genetic Code 3

It is universal.

- Evidence that all life evolved from a common ancestor
 - Different codons that specify the same amino acid are termed **synonymous codons**
 - Nonsynonymous codons** encode different amino acids

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Three at a Time

Size of a genetic code word (codon)

Original RNA sequence	GAC GAC GAC GAC GAC GAC ...
Amino acid sequence	Asp Asp Asp Asp Asp Asp ...
One base added	GAC G A CGA CGA CGA CGA ...
Amino acid sequence altered	Asp Gly Arg Arg Arg Arg ...
Two bases added	GAC UGG ACG ACG ACG ACG ...
Amino acid sequence altered	Asp Trp Thr Thr Thr Thr ...
Three bases added	GAC UUG GAC GAC GAC GAC ...
Amino acid sequence altered and then restored	Asp Leu Asp Asp Asp Asp ...

 = Wrong triplet

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Reading Frame

2nd reading frame
U G C C C A A G A
 Cys Pro Arg

AUG C C C A A G A C

1st reading frame
A U G C C C A A G
 Met Pro Lys

3rd reading frame
G C C C A A G A C
 Ala Gln Asp

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Translation—Building a Protein

Requires mRNA, tRNAs with amino acids, ribosomes, energy molecules (ATP, GTP) and protein factors

Divided into three steps:

- Initiation
- Elongation
- Termination

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Translation Initiation 1

- The leader sequence of the mRNA forms hydrogen bonds with the small ribosomal subunit.
- The start codon (AUG) attracts an initiator tRNA that carries methionine.
- This completes the **initiation complex**.

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Translation Initiation 2

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Translation Elongation 1

The large ribosomal subunit joins the initiation complex

The codon adjacent to the initiation codon then bonds to its complementary anticodon, which is part of a free tRNA that carries the second amino acid

- Two amino acids attached to their tRNAs align.

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Translation Elongation 2

Positions of the sites on the ribosome remain the same, cover different parts of the mRNA as the ribosome moves.

- The P site bears growing amino acid chain.
- The A site holds the next amino acid to be added to the chain.

Amino acids link by a peptide bond, with the help of rRNA that functions as a ribozyme.

The polypeptide builds one amino acid at a time.

- Each piece is brought in by a tRNA whose anticodon corresponds to a consecutive mRNA codon as the ribosome moves down the mRNA.

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Building a Polypeptide

(a) Second amino acid joins initiation complex.

(b) First peptide bond forms as new amino acid arrives.

(c) Amino acid chain extends.

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Translation Termination 1

- Occurs when a stop codon enters the A site of the ribosome
- A protein release factor frees the polypeptide
- The ribosomal subunits separate and are recycled
- New polypeptide is released

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Translation Termination 2

(a) Ribosome reaches stop codon.

(b) Components disassemble.

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Multiple Copies of a Protein Can Be Made Simultaneously

The closer to the end of the gene, the longer the polypeptide

5' → 3' mRNA

Ribosome

Polypeptide chain

Chaperone proteins

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Protein Structure

Proteins fold into one or more 3-D shapes or **conformations**

- Based on attraction and repulsion between atoms of proteins, and interactions of proteins with chemicals in the environment

There are four levels for protein structure:

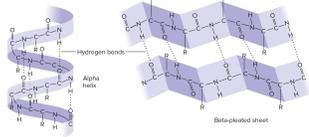
- **Primary (1^o) structure**
- **Secondary (2^o) structure**
- **Tertiary (3^o) structure**
- **Quaternary (4^o) structure**

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Four Levels of Protein Structure 1

H₂N - Ala - Thr - Ser - Tyr - Glu - Gly - COOH

(a) **Primary structure**—the sequence of amino acids in a polypeptide chain.



(b) **Secondary structure**—loops, coils, sheets, or other shapes formed by hydrogen bonds between neighboring carboxyl and amino groups.



(c) **Tertiary structure**—three-dimensional forms shaped by bonds between R groups, interactions between R groups and water.



(d) **Quaternary structure**—protein complexes formed by bonds between separate polypeptides.



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Four Levels of Protein Structure 2

(a) **Primary structure**—the sequence of amino acids in a polypeptide chain

(b) **Secondary structure**—loops, coils, sheets, or other shapes formed by hydrogen bonds between neighboring carboxyl and amino groups

(c) **Tertiary structure**—three dimensional forms shaped by bonds between R groups, interaction between R groups and water

(d) **Quaternary structure**—protein complexes formed by bonds between separate polypeptides

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Protein Folding 1

Proteins begin to fold after the amino acid chain winds away from the ribosome.

- First few amino acids in a protein secreted in a membrane form a "signal sequence."
 - Leads it and the ribosome into a pore in the ER membrane
 - Not found on proteins synthesized on free ribosomes

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Protein Folding 2

Various proteins assist in precise folding, whatever the destination

Chaperone proteins

- Stabilize partially folded regions in their correct form
- Prevent a protein from getting stuck in an intermediate form
- Developed into drugs to treat diseases that result from misfolded proteins

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Protein Misfolding 1

Misfolded proteins are tagged with ubiquitin.

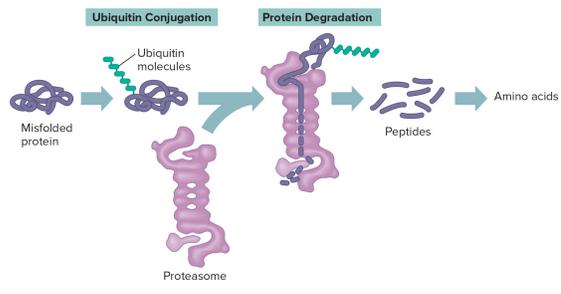
Protein with more than one tag is taken to a **proteasome**, a tunnel-like multiprotein structure.

- As the protein moves through the tunnel, it is straightened and dismantled.
- Proteasomes also destroy properly folded proteins that are in excess or no longer needed.

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Protein Misfolding 2



Ubiquitin Conjugation

Protein Degradation

Misfolded protein

Ubiquitin molecules

Proteasome

Peptides

Amino acids

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Diseases of Protein Misfolding 1

Proteins misfold from a mutation, or by having more than one conformation.

- A mutation alters the attractions and repulsions between parts of the protein.
- Prion protein can fold into any of several conformations.
 - Moreover, it can be passed on to other proteins upon contact, propagating like an infectious agent.

In several disorders that affect the brain, the misfolded proteins aggregate.

- The protein masses that form clog the proteasomes and inhibit their function.

Different proteins are affected in different disorders.

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Diseases of Protein Misfolding 2

Table 10.4 Diseases Associated with Protein Misfolding

Disease	Misfolded Protein(s)
Alzheimer disease	Amyloid beta precursor protein, tau proteins
Familial amyotrophic lateral sclerosis	Superoxide dismutase, TDP-43
Frontotemporal dementia	Tau proteins, TDP-43
Hereditary ATTR amyloidosis	Transthyretin
Huntington disease	Huntingtin
Parkinson disease	Alpha synuclein
Lewy body dementia	Alpha synuclein
PKU	Phenylalanine hydroxylase
Prion diseases	Prion protein

(All but Huntington disease are genetically heterogeneous; that is, abnormalities in different proteins cause similar syndromes.)

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Prion Diseases 1

- A subgroup of protein misfolding conditions
- They were first described in sheep, which develop a disease called scrapie
- More than 85 animal species develop similar diseases
- Prion diseases in humans are caused by either a mutation in the prion-related protein gene (PRPN) or transmissible prion protein (sporadic) in the rare conformation.

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Prion Diseases 2

Table 10.5 Prion Diseases of Humans

Disease	Symptoms
Creutzfeldt-Jakob disease	Memory loss, nervousness, trembling hands, blank facial expression, jerky movements, unsteady gait, personality changes, anxiety, depression, impaired thinking, insomnia, visual loss, difficulty speaking and swallowing, coma, with death from heart failure, pneumonia, or infections within a year.
Fatal familial insomnia	Progressive inability to sleep and vivid dreams during scant sleep. Physical and mental deterioration, coma, death within a few months.
Gerstmann-Straussler disease	Memory loss, dementia, ataxia (uncoordinated movement), amyloid plaques in the brain. Death within 7 years.

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Prion Diseases 3

The first prion disease recognized in humans was kuru

- Affected the native Fore people who lived in the remote mountains of Papua New Guinea
- Was traced to a ritual in which the people ate their war heroes



The Nobel Foundation, 1976

Another is *variant* Creutzfeldt-Jacob disease (CJD)

- Popularly called mad cow disease

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How Prions Cause Disease 1

Prions cause disease both by spreading the alternate form (infectious or mutant) and by aggregation of the protein.

The normal function of prion protein is not well understood.

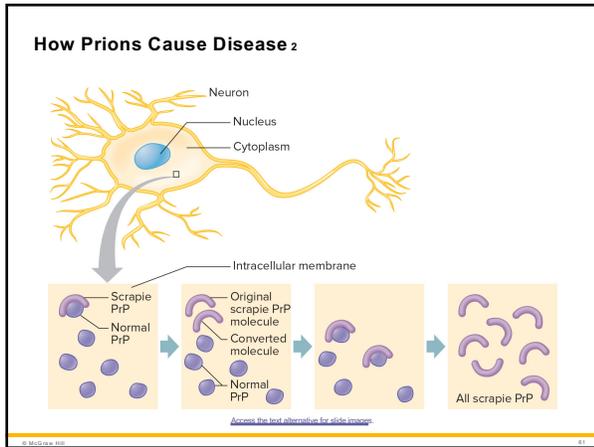
- May be important in protecting the nervous system

All prion diseases are diseases of protein folding

- The infectious forms have beta-pleated sheets in places where their normal counterparts have alpha helices.

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