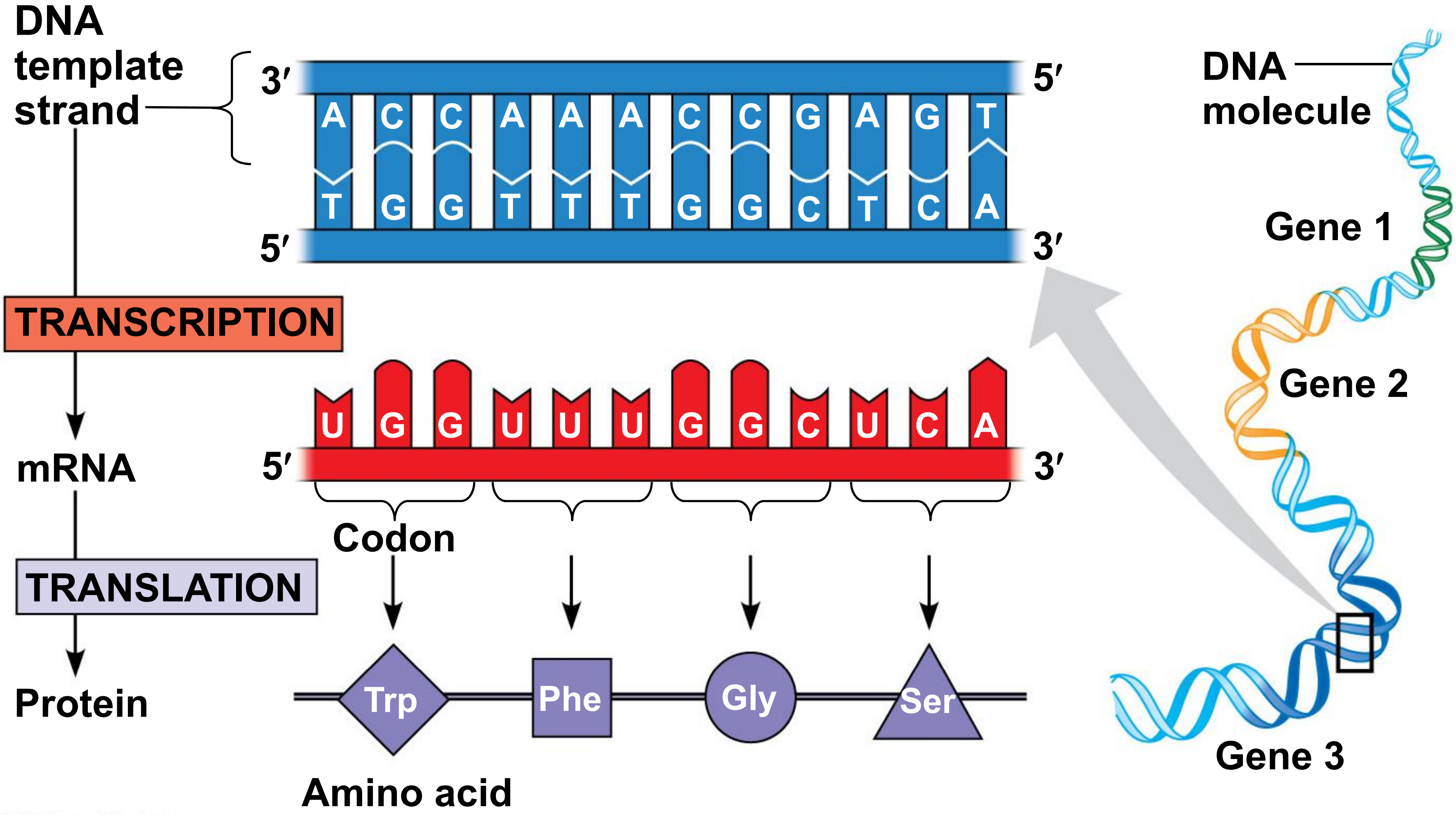
The Genetic Code

- There are 20 amino acids, but there are only four nucleotide bases in DNA
- The flow of information from gene to protein is based on a **triplet code**: a series of non-overlapping, three-nucleotide words
- The words of a gene are transcribed into complementary non-overlapping three-nucleotide words of mRNA
- These words are then translated into a chain of amino acids, forming a polypeptide


DNA template strand
3′
A C C A A A C C G A G T
T G G T T T G G C T C A
5′
5′
3′
TRANSCRIPTION
mRNA
5′
U G G U U U G G C U C A
3′
Codon
TRANSLATION
Protein
Trp
Phe
Gly
Ser
Amino acid
DNA molecule
Gene 1
Gene 2
Gene 3

- During transcription, one of the two DNA strands, called the **template strand,** provides a template for ordering the sequence of complementary nucleotides in an RNA transcript
- The template strand is always the same strand for a given gene
- During translation, the mRNA base triplets, called **codons**, are read in the 5′ to 3′ direction

- Codons along an mRNA molecule are read by translation machinery in the 5′ to 3′ direction
- Each codon specifies the amino acid (one of 20) to be placed at the corresponding position along a polypeptide

- All 64 codons were discovered by the mid-1960s
- Of the 64 triplets, 61 code for amino acids; 3 triplets are “stop” signals to end translation
- The genetic code is redundant (more than one codon may specify a particular amino acid) but not ambiguous; no codon specifies more than one amino acid
- Codons must be read in the correct **reading frame** (correct groupings) in order for the specified polypeptide to be produced

Second mRNA base

First mRNA base (5′ end of codon)	U	C	A	G	Third mRNA base (3′ end of codon)
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC	UCC	UAC	UGC	C
	UUA Leu	UCA	UAA Stop	UGA Stop	A
	UUG	UCG	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC	CCC	CAC	CGC	C
	CUA	CCA	CAA Gln	CGA	A
	CUG	CCG	CAG	CGG	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC	ACC	AAC	AGC	C
	AUA	ACA	AAA Lys	AGA Arg	A
	AUG Met or start	ACG	AAG	AGG	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC	GCC	GAC	GGC	C
	GUA	GCA	GAA Glu	GGA	A
	GUG	GCG	GAG	GGG	G

- The genetic code is nearly universal, shared by the simplest bacteria to the most complex animals
- Genes can be transcribed and translated after being transplanted from one species to another

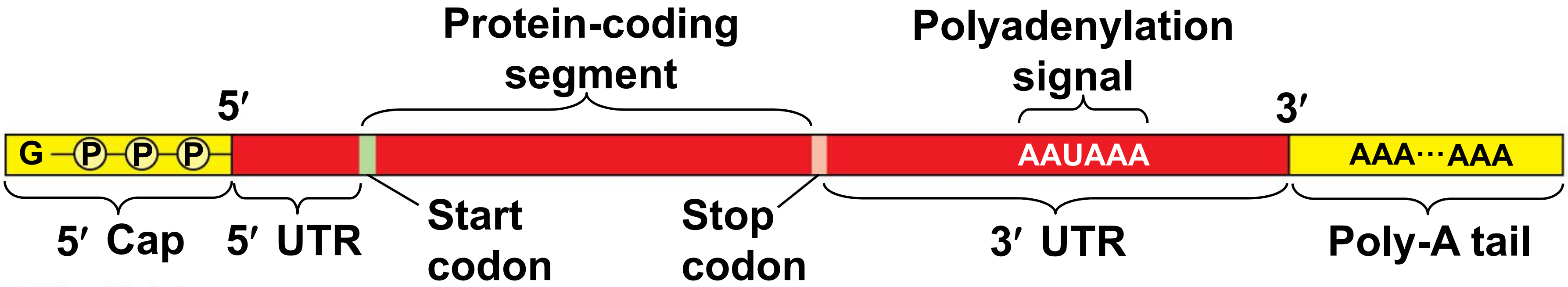
Eukaryotic cells modify RNA after transcription

- Enzymes in the eukaryotic nucleus modify pre-mRNA (**RNA processing**) before the genetic messages are dispatched to the cytoplasm
- During RNA processing, both ends of the primary transcript are usually altered
- Also, usually some interior parts of the molecule are cut out, and the other parts spliced together

Alteration of mRNA Ends

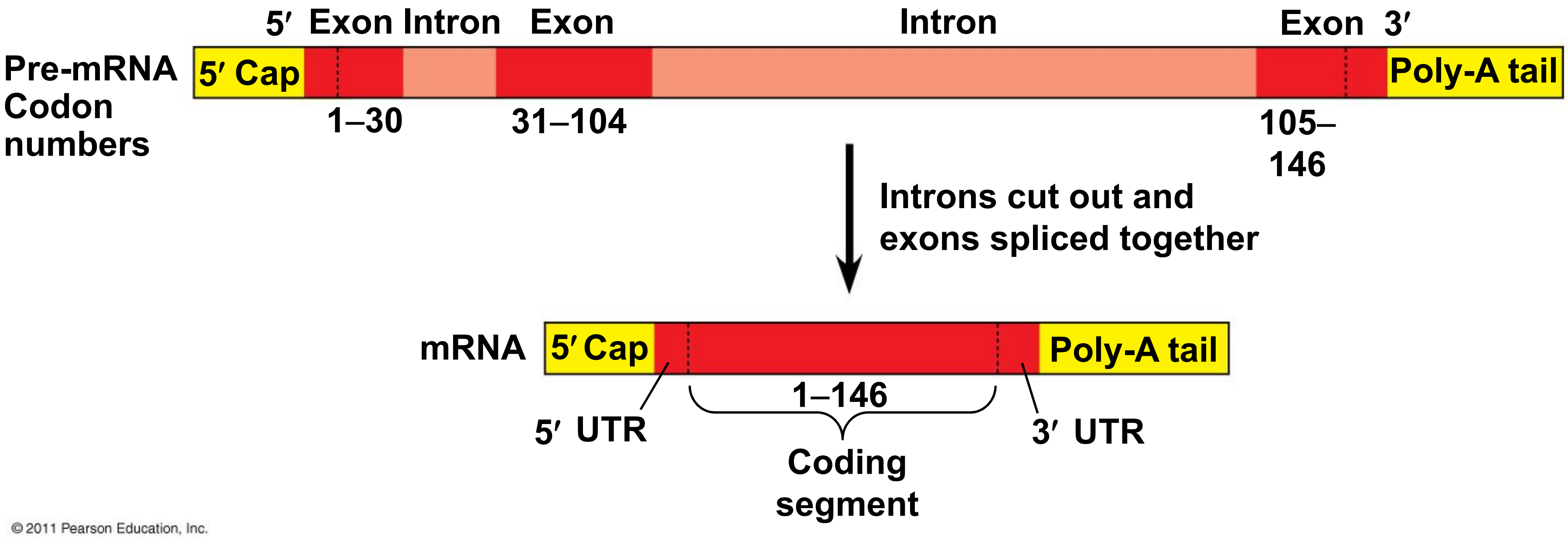
- Each end of a pre-mRNA molecule is modified in a particular way
  - The 5′ end receives a modified nucleotide **5′ cap**
  - The 3′ end gets a **poly-A tail**
- These modifications share several functions
  - They seem to facilitate the export of mRNA to the cytoplasm
  - They protect mRNA from hydrolytic enzymes
  - They help ribosomes attach to the 5′ end

Figure 17.10

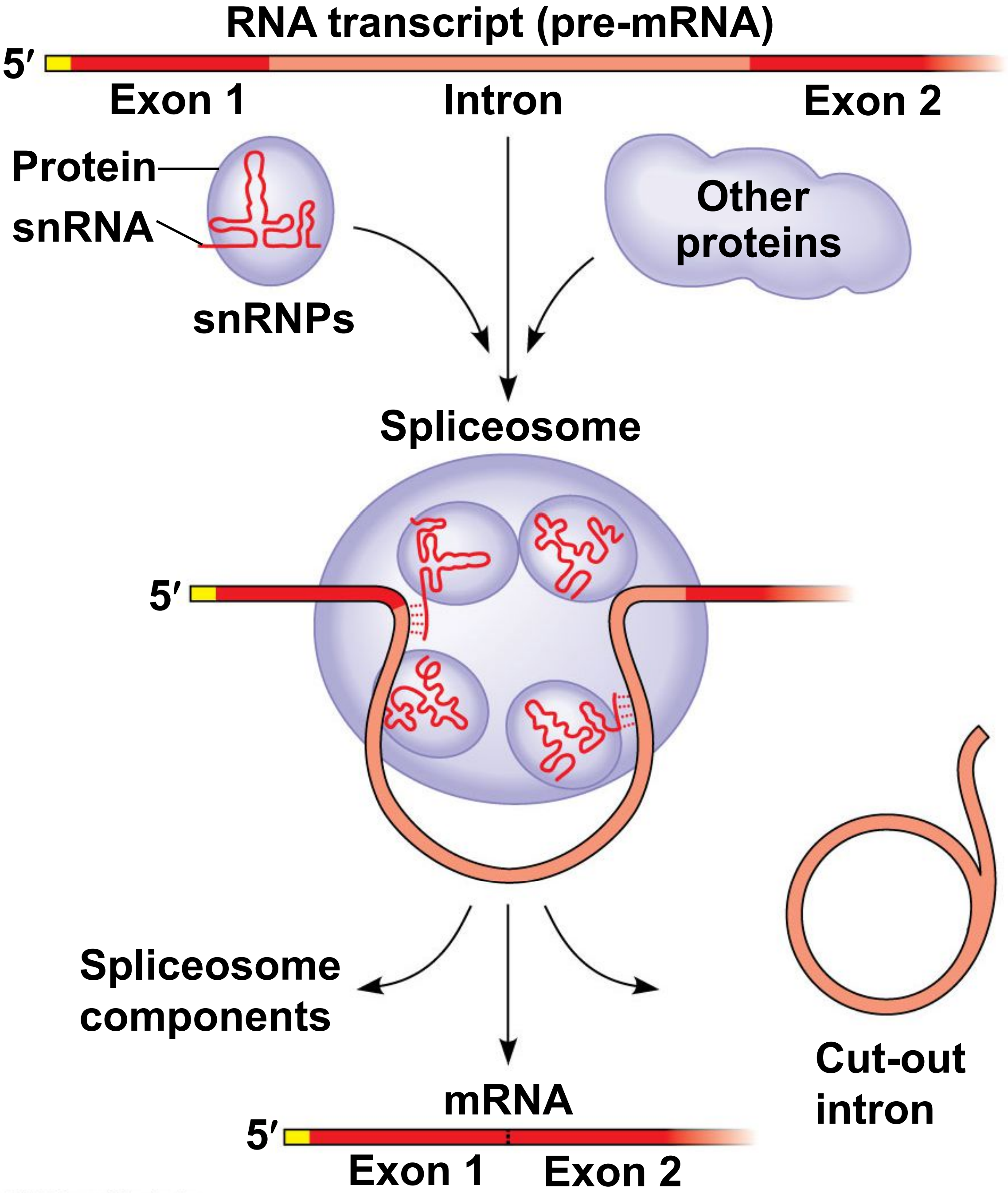

Protein-coding segment
Polyadenylation signal
5′
3′
G
P
P
P
AAUAAA
AAA···AAA
5′ Cap
5′ UTR
Start codon
Stop codon
3′ UTR
Poly-A tail

Split Genes and RNA Splicing

- Most eukaryotic genes and their RNA transcripts have long noncoding stretches of nucleotides that lie between coding regions
- These noncoding regions are called intervening sequences, or **introns**
- The other regions are called **exons** because they are eventually expressed, usually translated into amino acid sequences
- **RNA splicing** removes introns and joins exons, creating an mRNA molecule with a continuous coding sequence


5′
Exon
Intron
Exon
Intron
Exon
3′
Pre-mRNA
5′ Cap
Poly-A tail
Codon numbers
1–30
31–104
105–146
Introns cut out and exons spliced together
mRNA
5′ Cap
Poly-A tail
5′ UTR
1–146
3′ UTR
Coding segment

- In some cases, RNA splicing is carried out by spliceosomes
- **Spliceosomes** consist of a variety of proteins and several small nuclear ribonucleoproteins (snRNPs) that recognize the splice sites



RNA transcript (pre-mRNA)

5′

Exon 1

Intron

Exon 2

Protein

snRNA

snRNPs

Other proteins

Spliceosome

5′

Spliceosome components

Cut-out intron

mRNA

5′

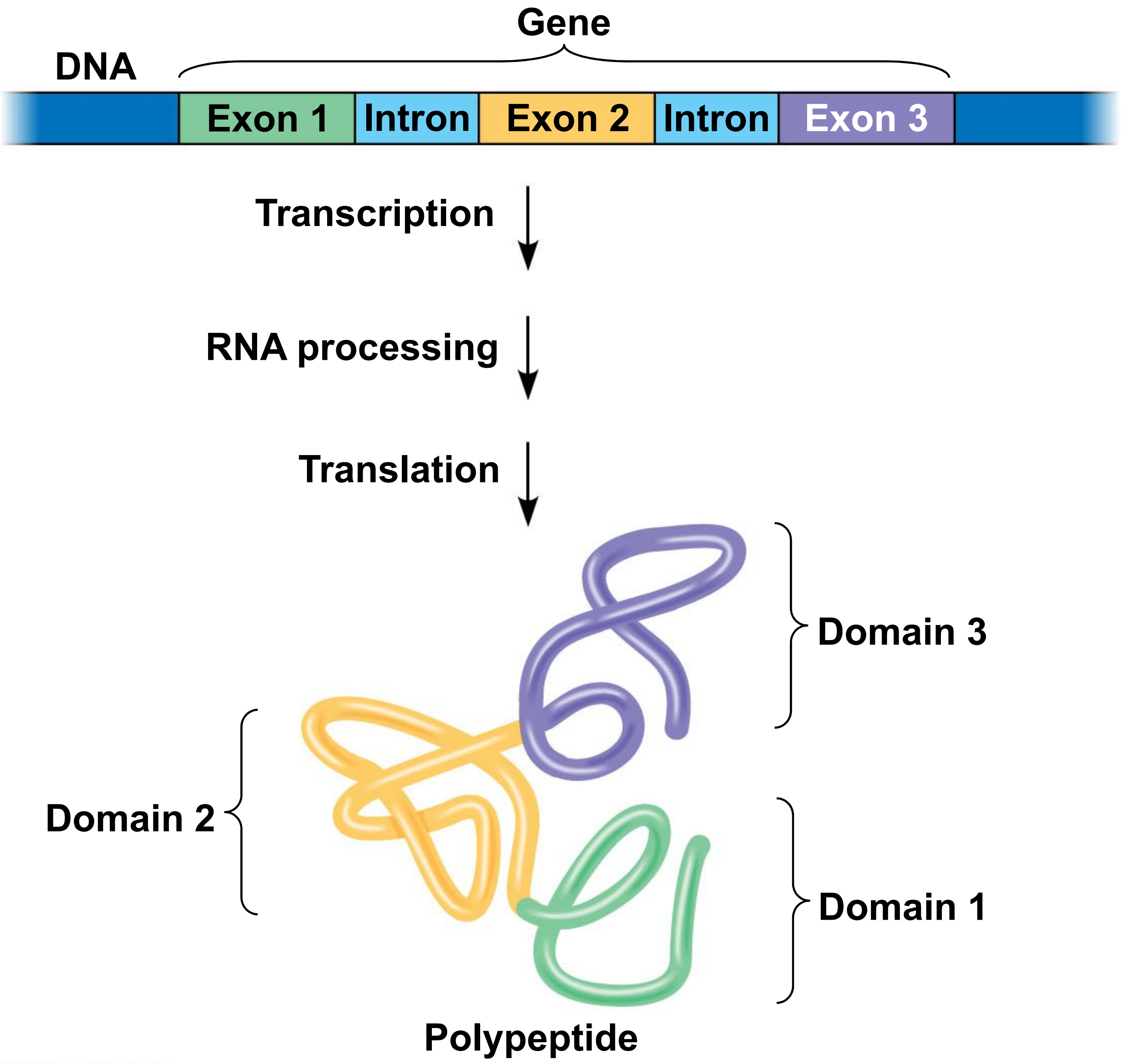
Exon 1

Exon 2

Ribozymes

- **Ribozymes** are catalytic RNA molecules that function as enzymes and can splice RNA
- The discovery of ribozymes rendered obsolete the belief that all biological catalysts were proteins

Figure 17.13



Gene

DNA

Exon 1 | Intron | Exon 2 | Intron | Exon 3

Transcription

RNA processing

Translation

Domain 3

Domain 2

Domain 1

Polypeptide

Translation is the RNA-directed synthesis of a polypeptide

- Genetic information flows from mRNA to protein through the process of translation

Molecular Components of Translation

- A cell translates an mRNA message into protein with the help of **transfer RNA (tRNA)**
- tRNAs transfer amino acids to the growing polypeptide in a ribosome
- Translation is a complex process in terms of its biochemistry and mechanics

The Structure and Function of Transfer RNA

- Molecules of tRNA are not identical
  - Each carries a specific amino acid on one end
  - Each has an **anticodon** on the other end; the anticodon base-pairs with a complementary codon on mRNA
- A tRNA molecule consists of a single RNA strand that is only about 80 nucleotides long
- Flattened into one plane to reveal its base pairing, a tRNA molecule looks like a cloverleaf

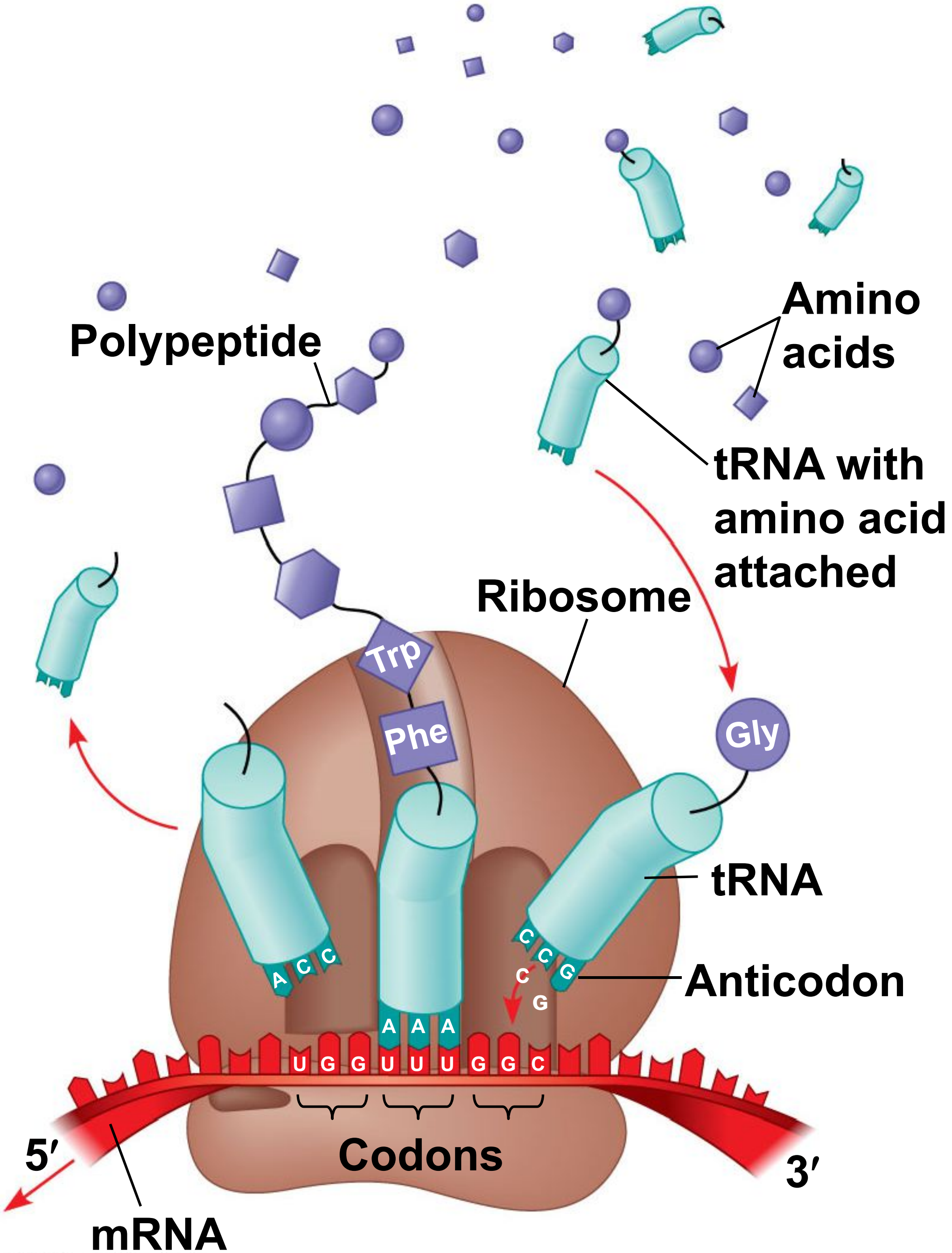
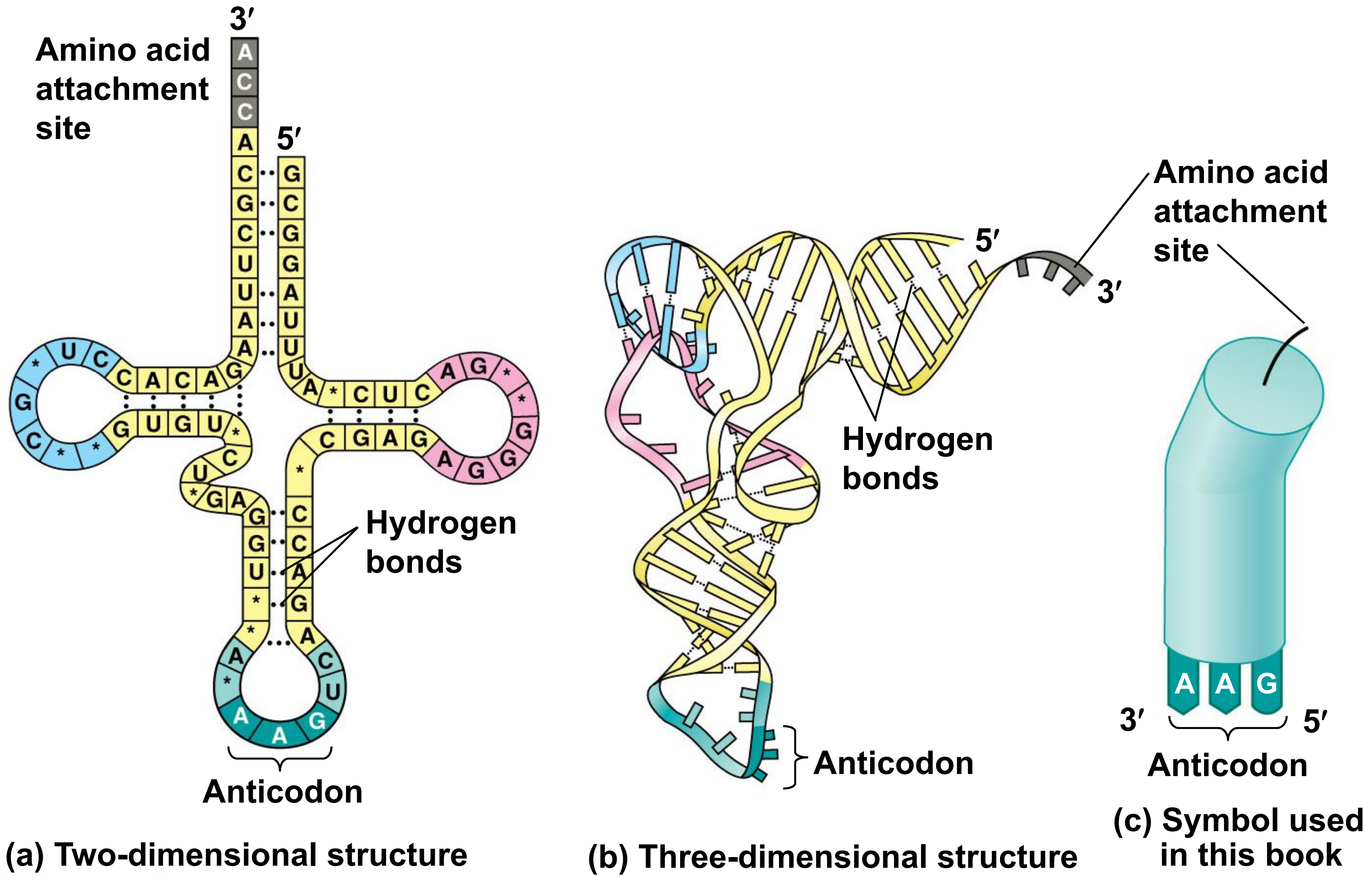

Polypeptide
Amino acids
tRNA with amino acid attached
Ribosome
Trp
Phe
Gly
tRNA
A C C
A A A
C C G
C
G
Anticodon
U G G U U U G G C
Codons
5′
3′
mRNA

Figure 17.15

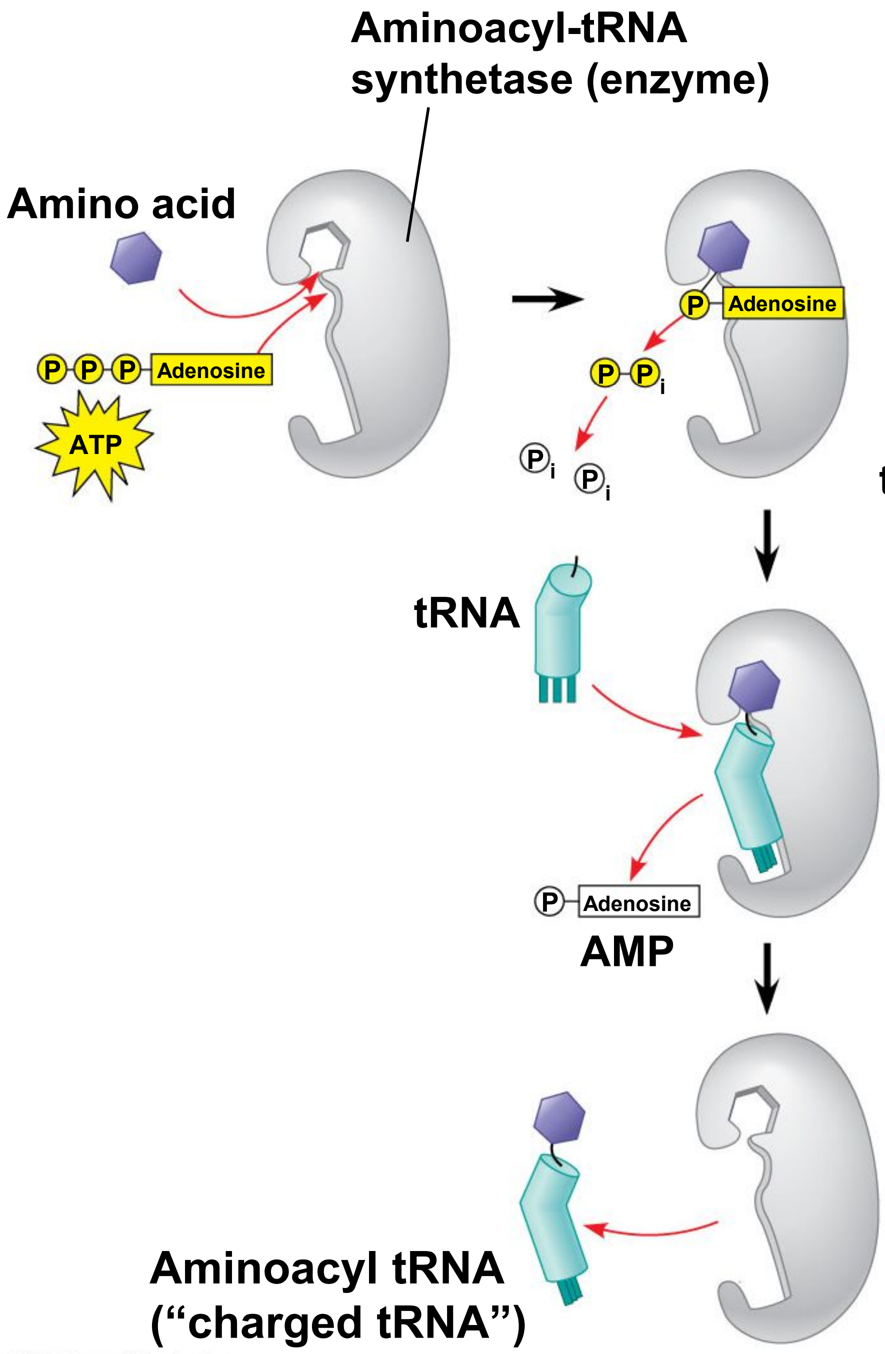


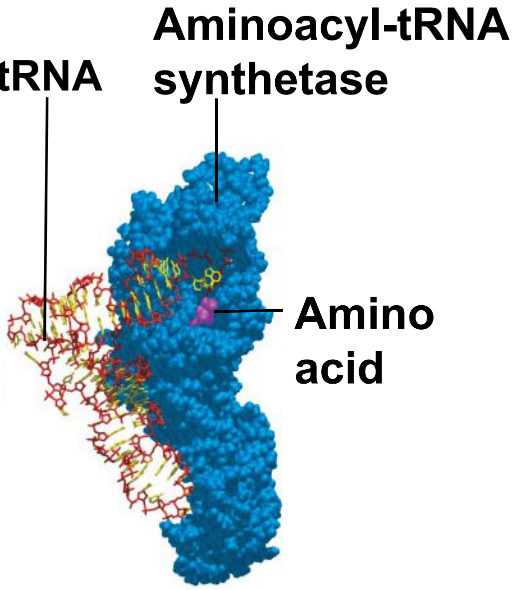
(a) Two-dimensional structure

(b) Three-dimensional structure

(c) Symbol used in this book

- Accurate translation requires two steps
  - First: a correct match between a tRNA and an amino acid, done by the enzyme **aminoacyl-tRNA synthetase**
  - Second: a correct match between the tRNA anticodon and an mRNA codon
- Flexible pairing at the third base of a codon is called **wobble** and allows some tRNAs to bind to more than one codon

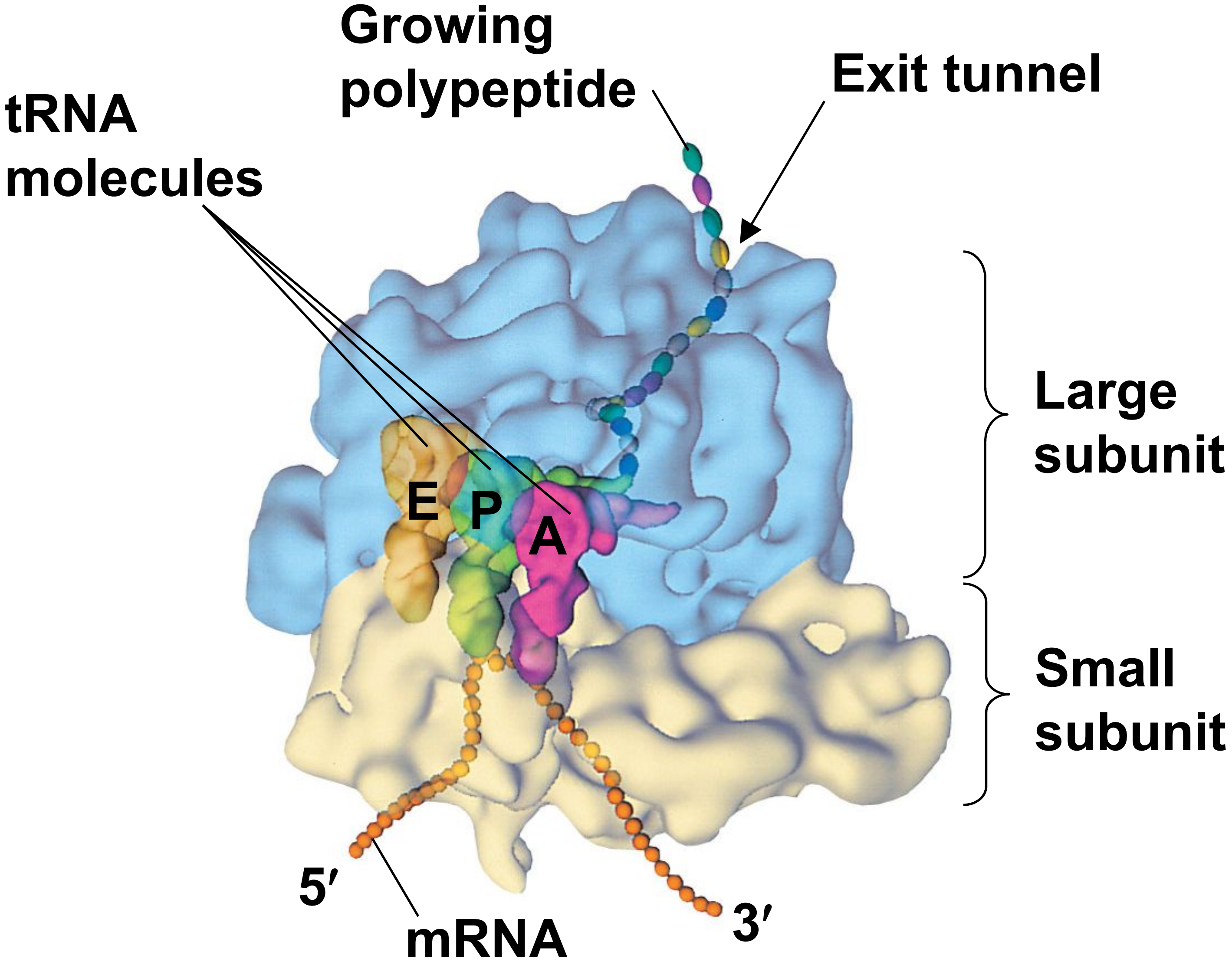




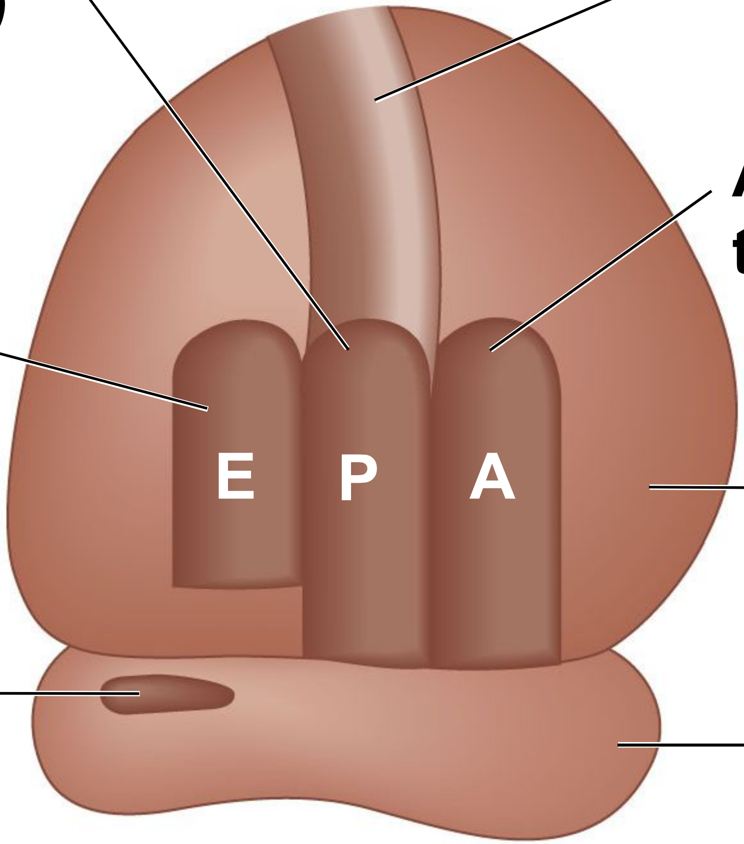
Computer model

Ribosomes

- Ribosomes facilitate specific coupling of tRNA anticodons with mRNA codons in protein synthesis
- The two ribosomal subunits (large and small) are made of proteins and **ribosomal RNA (rRNA)**
- Bacterial and eukaryotic ribosomes are somewhat similar but have significant differences



(a) Computer model of functioning ribosome



P site (Peptidyl-tRNA binding site)

Exit tunnel

A site (Aminoacyl-tRNA binding site)

E site (Exit site)

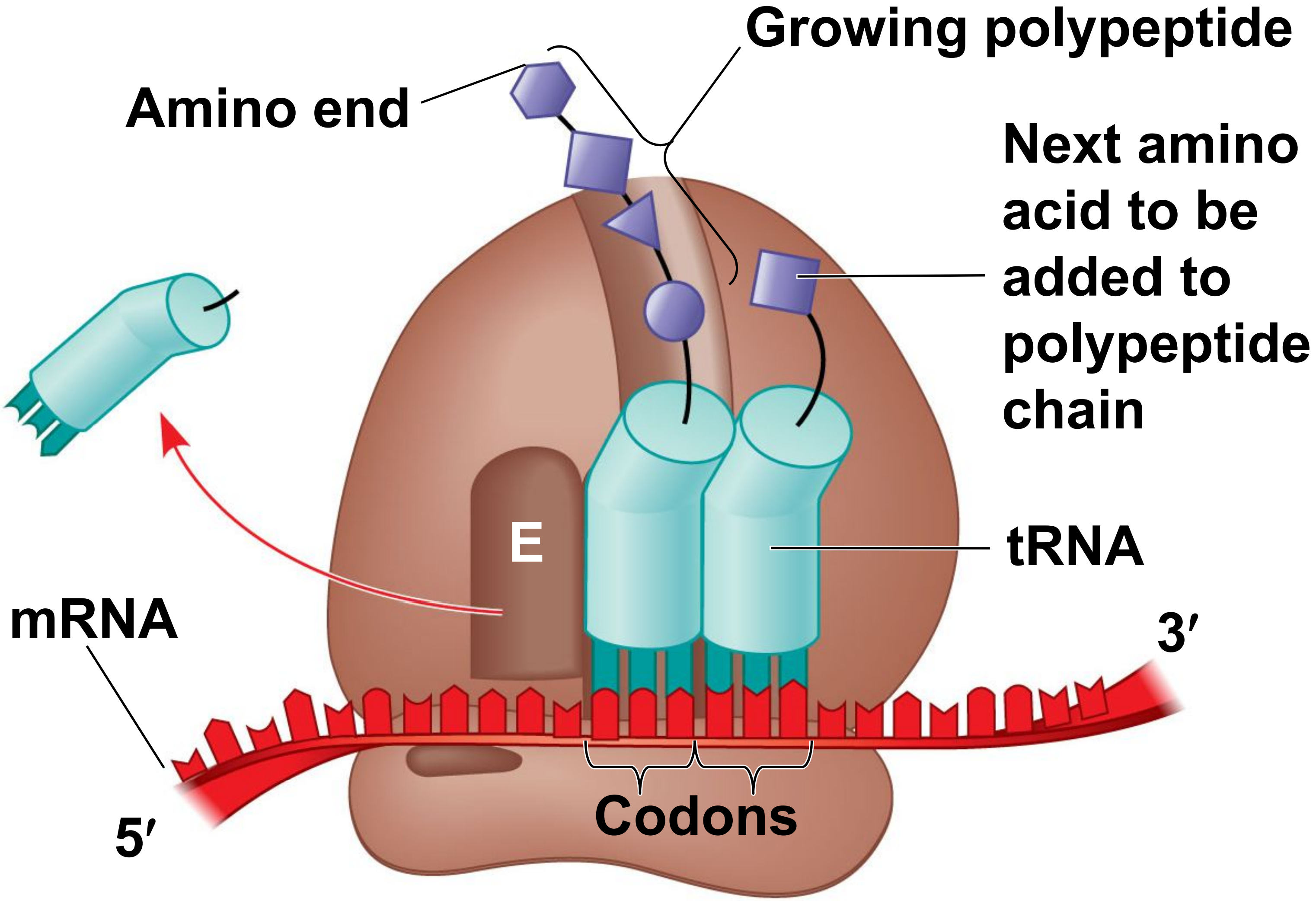
Large subunit

mRNA binding site

Small subunit

(b) Schematic model showing binding sites

Figure 17.17c



(c) Schematic model with mRNA and tRNA

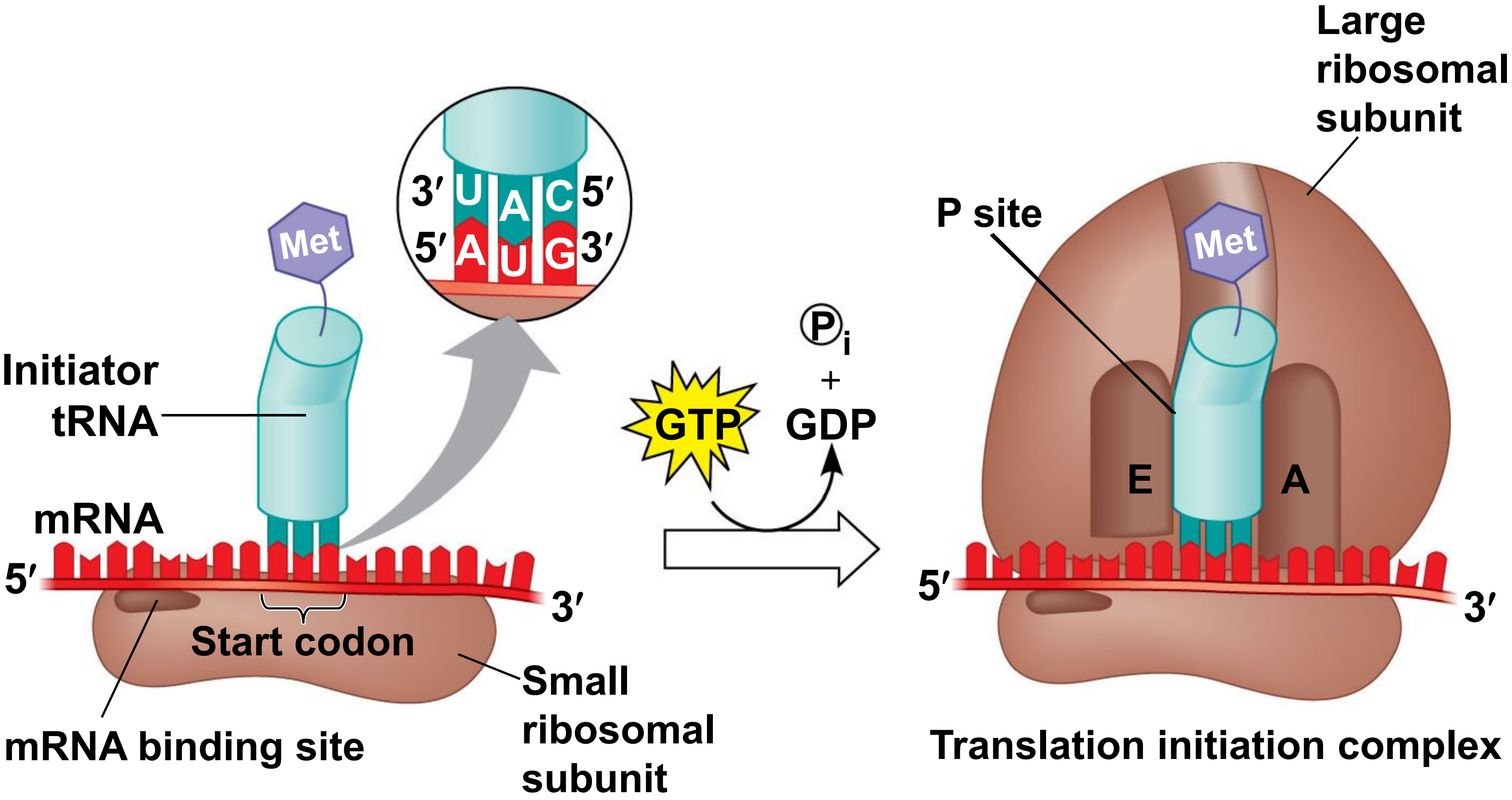
- A ribosome has three binding sites for tRNA
  - The **P site** holds the tRNA that carries the growing polypeptide chain
  - The **A site** holds the tRNA that carries the next amino acid to be added to the chain
  - The **E site** is the exit site, where discharged tRNAs leave the ribosome

Building a Polypeptide

- The three stages of translation
  - Initiation
  - Elongation
  - Termination
- All three stages require protein “factors” that aid in the translation process

Ribosome Association and Initiation of Translation

- The initiation stage of translation brings together mRNA, a tRNA with the first amino acid, and the two ribosomal subunits
- First, a small ribosomal subunit binds with mRNA and a special initiator tRNA
- Then the small subunit moves along the mRNA until it reaches the start codon (AUG)
- Proteins called initiation factors bring in the large subunit that completes the translation initiation complex

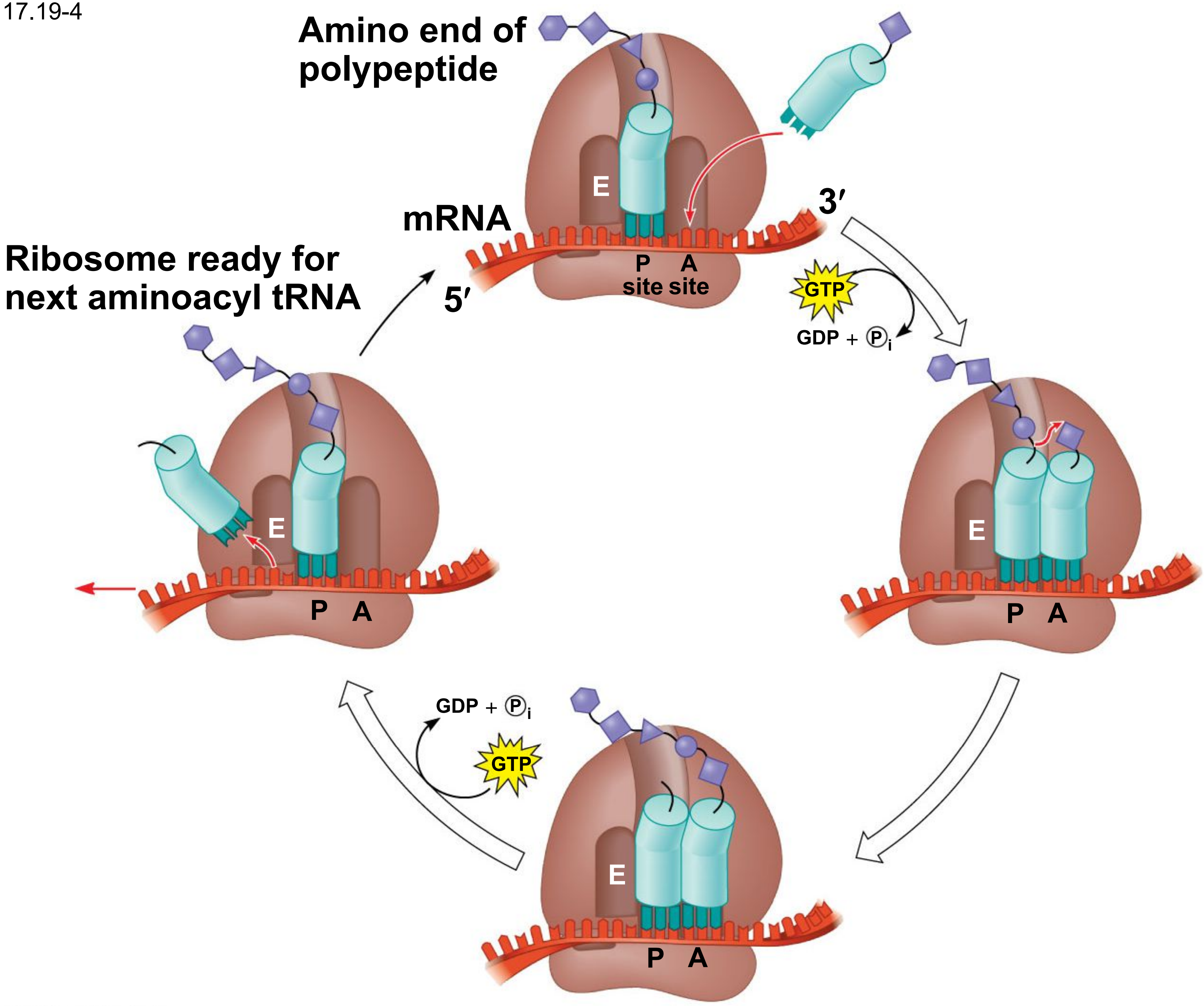


Translation initiation complex

Elongation of the Polypeptide Chain

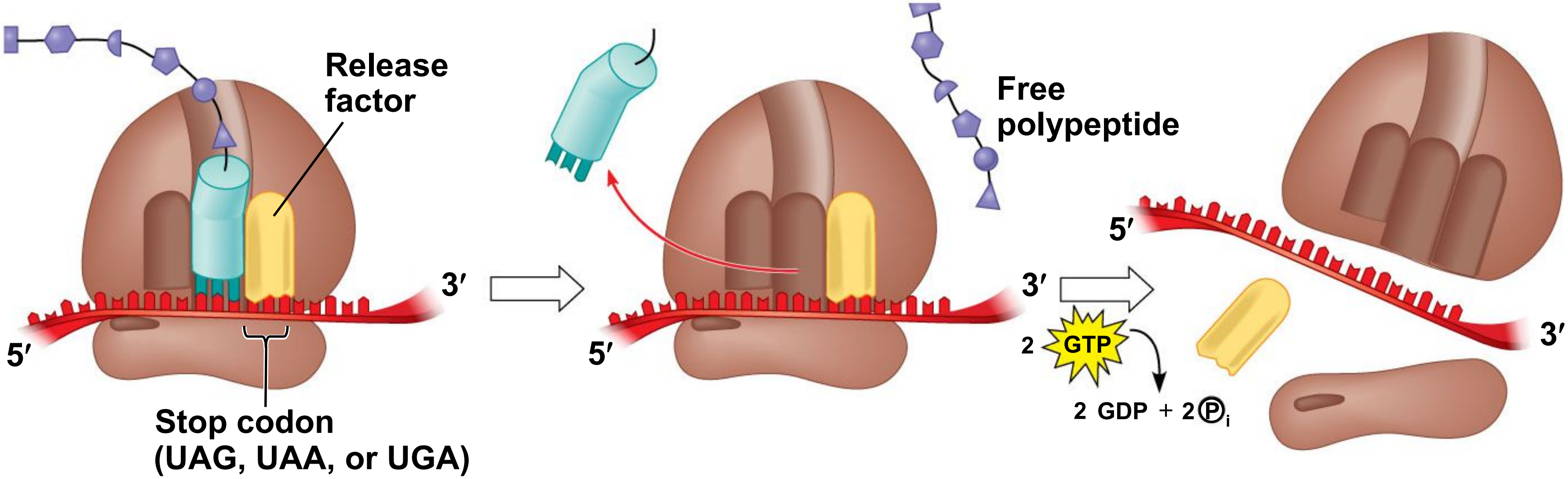
- During the elongation stage, amino acids are added one by one to the preceding amino acid at the C-terminus of the growing chain
- Each addition involves proteins called elongation factors and occurs in three steps: codon recognition, peptide bond formation, and translocation
- Translation proceeds along the mRNA in a 5′ to 3′ direction

Figure 17.19-4



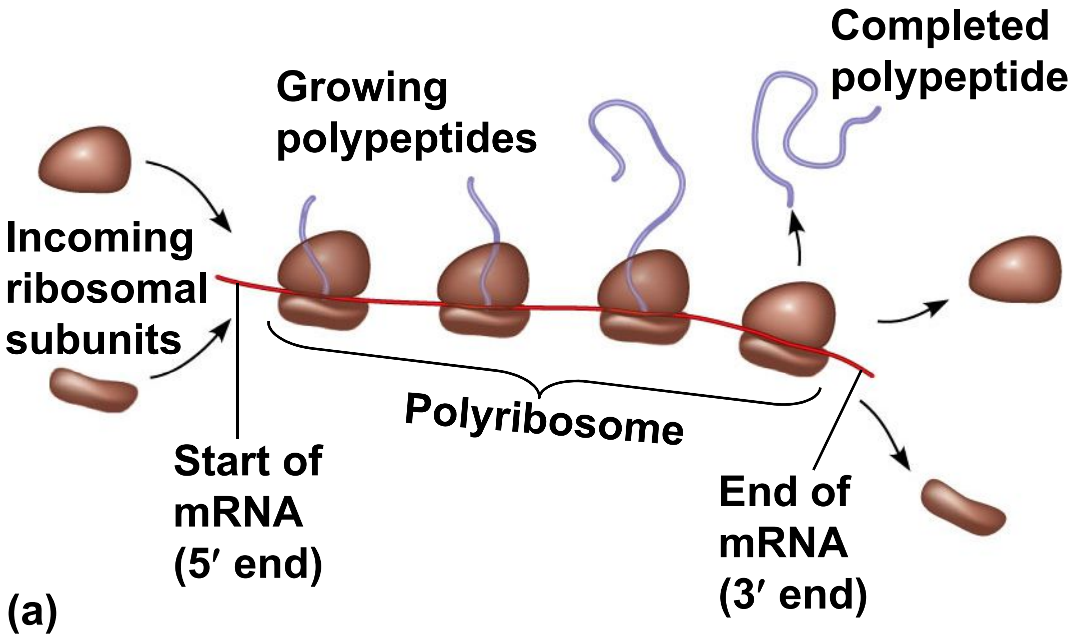
Termination of Translation

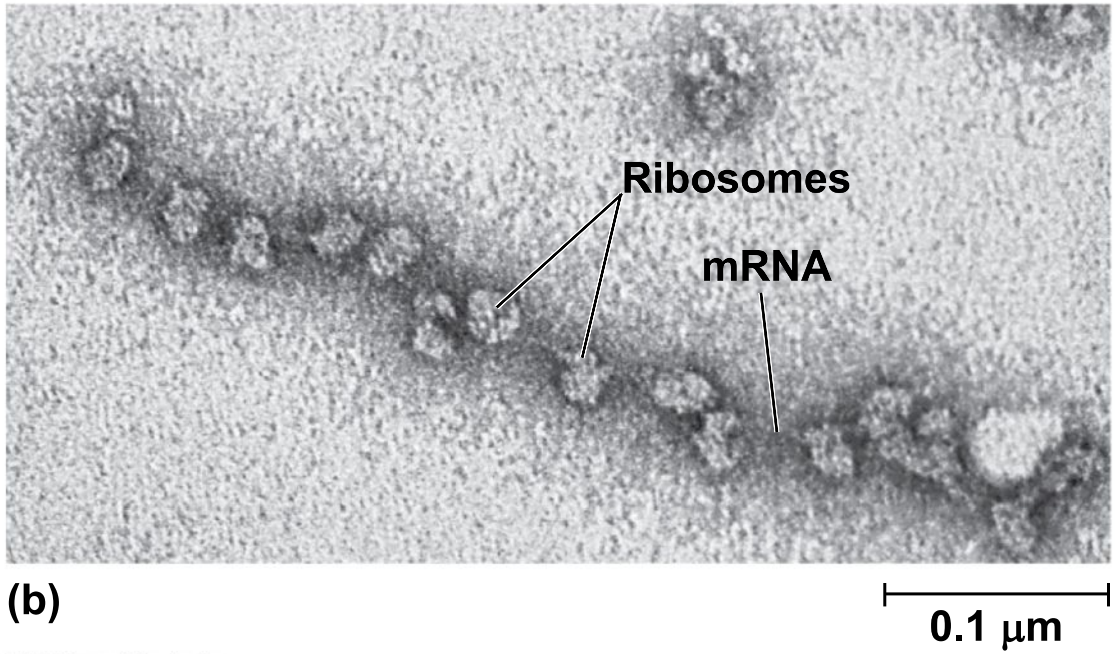
- Termination occurs when a stop codon in the mRNA reaches the A site of the ribosome
- The A site accepts a protein called a release factor
- The release factor causes the addition of a water molecule instead of an amino acid
- This reaction releases the polypeptide, and the translation assembly then comes apart


Release factor
3′
5′
Stop codon (UAG, UAA, or UGA)
Free polypeptide
3′
5′
2 GTP
2 GDP + 2 Ⓟi
5′
3′

Polyribosomes

- A number of ribosomes can translate a single mRNA simultaneously, forming a **polyribosome** (or **polysome**)
- Polyribosomes enable a cell to make many copies of a polypeptide very quickly


Completed polypeptide
Growing polypeptides
Incoming ribosomal subunits
Polyribosome
Start of mRNA (5′ end)
End of mRNA (3′ end)
(a)


Ribosomes
mRNA
(b)
0.1 μm

Completing and Targeting the Functional Protein

- Often translation is not sufficient to make a functional protein
- Polypeptide chains are modified after translation or targeted to specific sites in the cell

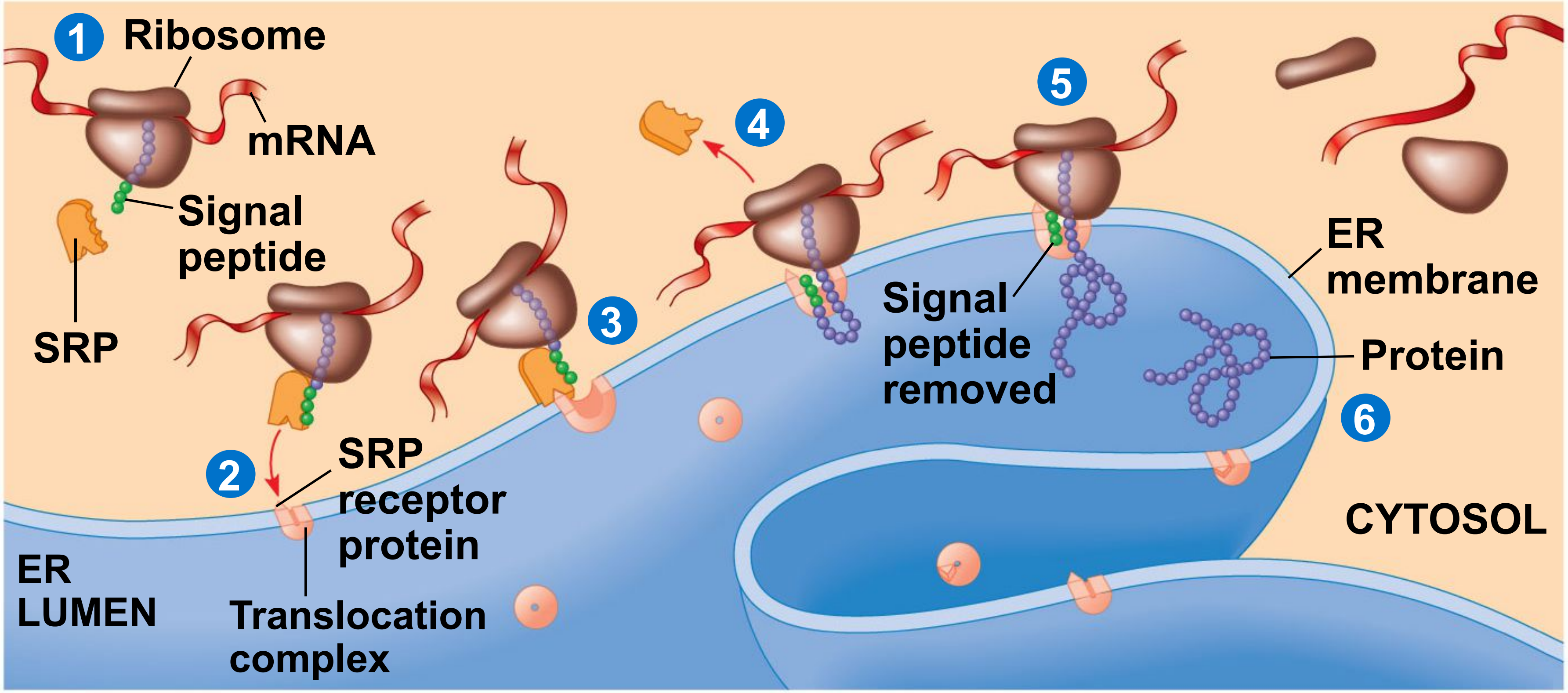
Protein Folding and Post-Translational Modifications

- During and after synthesis, a polypeptide chain spontaneously coils and folds into its three-dimensional shape
- Proteins may also require post-translational modifications before doing their job
- Some polypeptides are activated by enzymes that cleave them
- Other polypeptides come together to form the subunits of a protein

Targeting Polypeptides to Specific Locations

- Two populations of ribosomes are evident in cells: free ribsomes (in the cytosol) and bound ribosomes (attached to the ER)
- Free ribosomes mostly synthesize proteins that function in the cytosol
- Bound ribosomes make proteins of the endomembrane system and proteins that are secreted from the cell
- Ribosomes are identical and can switch from free to bound

- Polypeptide synthesis always begins in the cytosol
- Synthesis finishes in the cytosol *unless* the polypeptide signals the ribosome to attach to the ER
- Polypeptides destined for the ER or for secretion are marked by a **signal peptide**
- A **signal-recognition particle (SRP)** binds to the signal peptide
- The SRP brings the signal peptide and its ribosome to the ER


1
Ribosome
mRNA
Signal peptide
SRP
2
SRP receptor protein
Translocation complex
3
4
5
Signal peptide removed
ER membrane
Protein
6
CYTOSOL
ER LUMEN