

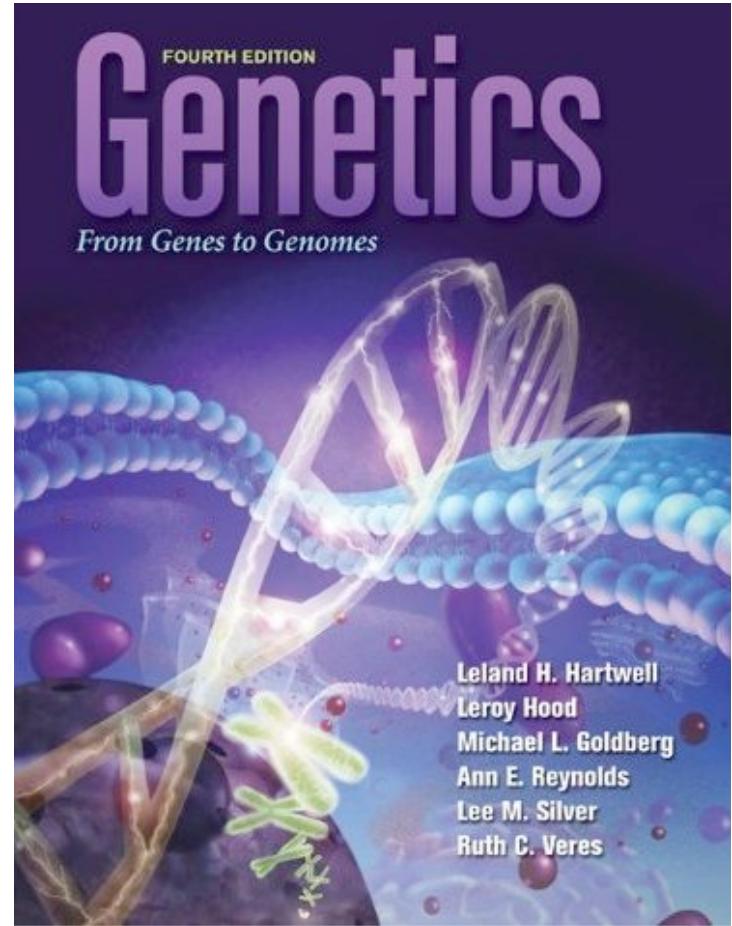
PowerPoint to accompany

Genetics: From Genes to Genomes

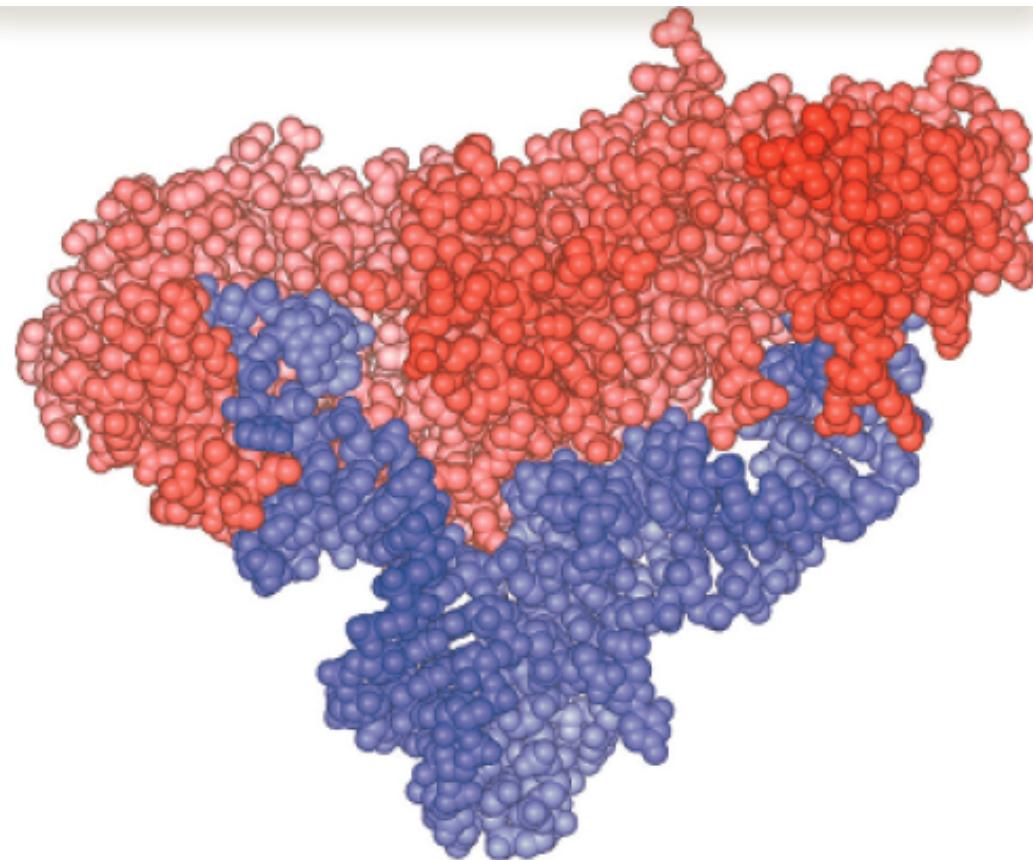
Fourth Edition

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Gene Expression: The Flow of Information from DNA to RNA to Protein



CHAPTER OUTLINE

- **Gene Expression: The Flow of Information from DNA to RNA to Protein**
- 8.1 The Genetic Code
- 8.2 Transcription: From DNA to RNA
- 8.3 Translation: From mRNA to Protein
- 8.4 Differences in Gene Expression Between Prokaryotes and Eukaryotes
- 8.5 The Effect of Mutations on Gene Expression and Gene Function

Four general themes for gene expression

Pairing of complementary bases is the key to the transfer of information from DNA to RNA and from RNA to protein

Polarities of DNA, RNA, and polypeptides help guide the mechanisms of gene expression

Gene expression requires input of energy and participation of specific proteins and macromolecular assemblies

Mutations that change genetic information or obstruct the flow of its expression can have dramatic effects on phenotype

Gene expression: the flow of genetic information from DNA via RNA to protein

RNA polymerase transcribes DNA to produce an RNA transcript

Ribosomes translate the mRNA sequence to synthesize a polypeptide

Translation follows the "genetic code"

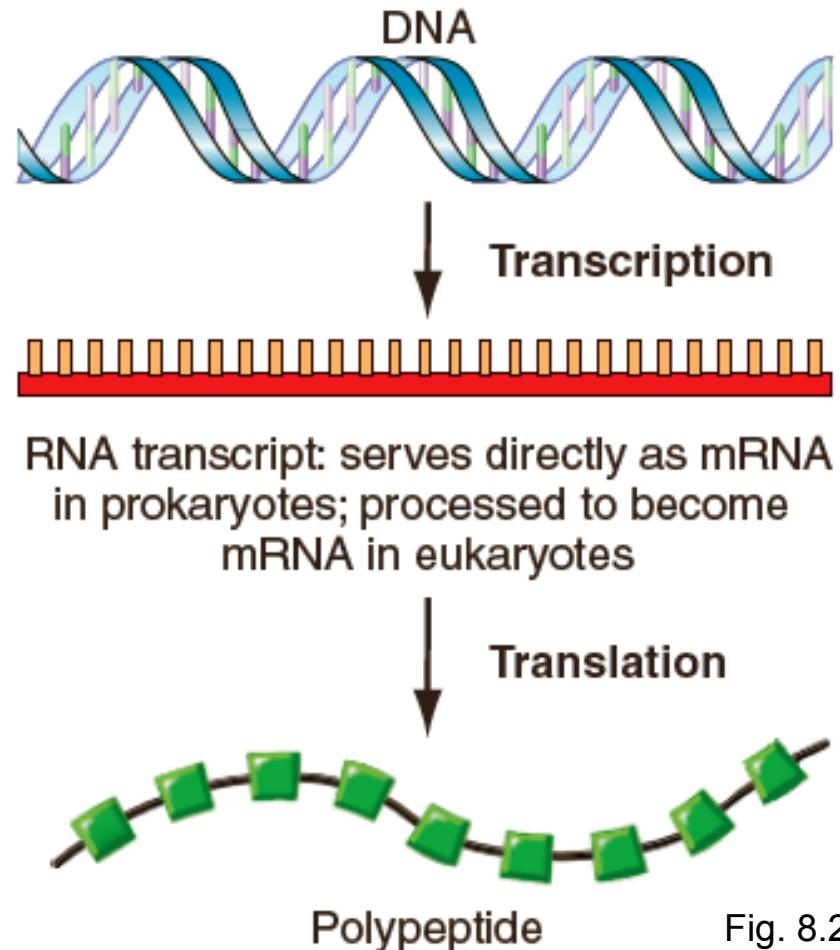


Fig. 8.2

Triplet codons of nucleotides represent individual amino acids

61 codons represent the 20 amino acids

3 codons signify stop

		Second letter					
		U	C	A	G		
First letter	U	UUU UUC UUA UUG	UCU UCC UCA UCG	UAU UAC UAA UAG	Tyr Stop Stop	UGU UGC UGA UGG	Cys Stop Trp
	C	CUU CUC CUA CUG	CCU CCC CCA CCG	CAU CAC CAA CAG	His Pro Gln	CGU CGC CGA CGG	U C A G
	A	AUU AUC AUA AUG	ACU ACC ACA ACG	AAU AAC AAA AAG	Asn Thr Lys	AGU AGC AGA AGG	U C A G
	G	GUU GUC GUA GUG	GCU GCC GCA GCG	GAU GAC GAA GAG	Asp Ala Glu	GGU GGC GGA GGG	U C A G
Third letter							

Fig. 8.3

A gene's nucleotide sequence is colinear with the amino acid sequence of the encoded polypeptide

Charles Yanofsky – deduced key features of relationship between nucleotides and amino acids

Generated large number of *trp*⁻ auxotrophic mutants in *E. coli*

Detailed analysis of mutations in *trpA* gene

- *TrpA* encodes a subunit of tryptophan synthetase
- Fine structure genetic map of *trpA* gene based on intragenic recombination
- Determined amino acid sequences of mutant tryptophan synthetase

Mutations in a gene are colinear with the sequence of amino acids in the encoded polypeptide

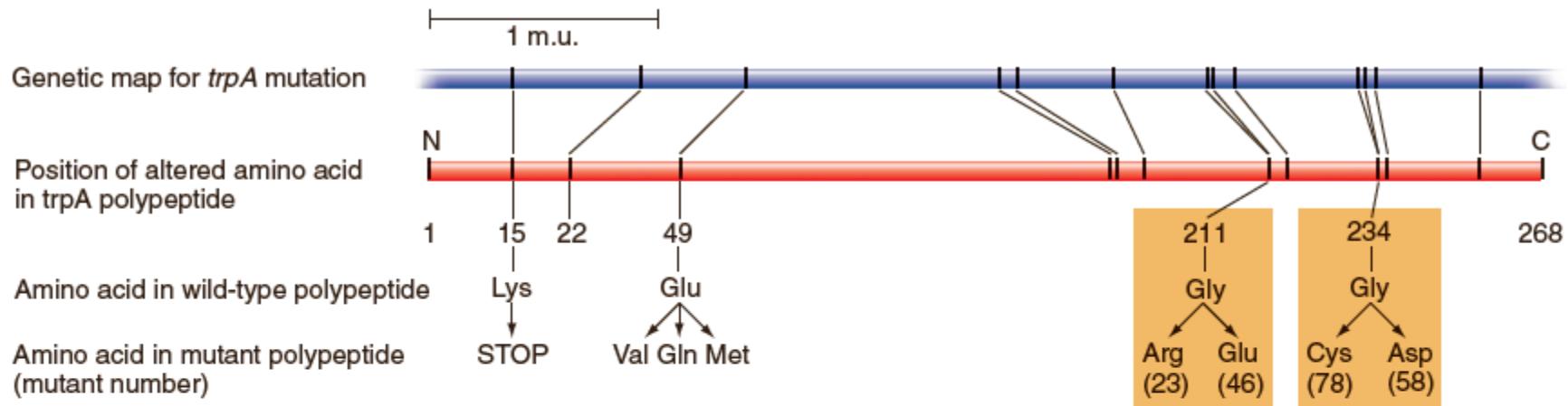


Fig. 8.4a

Different point mutations may affect the same amino acid

- Codons must contain >1 nucleotide

Each point mutation affects only one amino acid

- Each nucleotide is part of only one codon

Evidence that codons must contain two or more base pairs

Intragenic recombination

Wild-type allele can be produced by crossing two mutant strains with different amino acids at the same position

Recombination within a codon

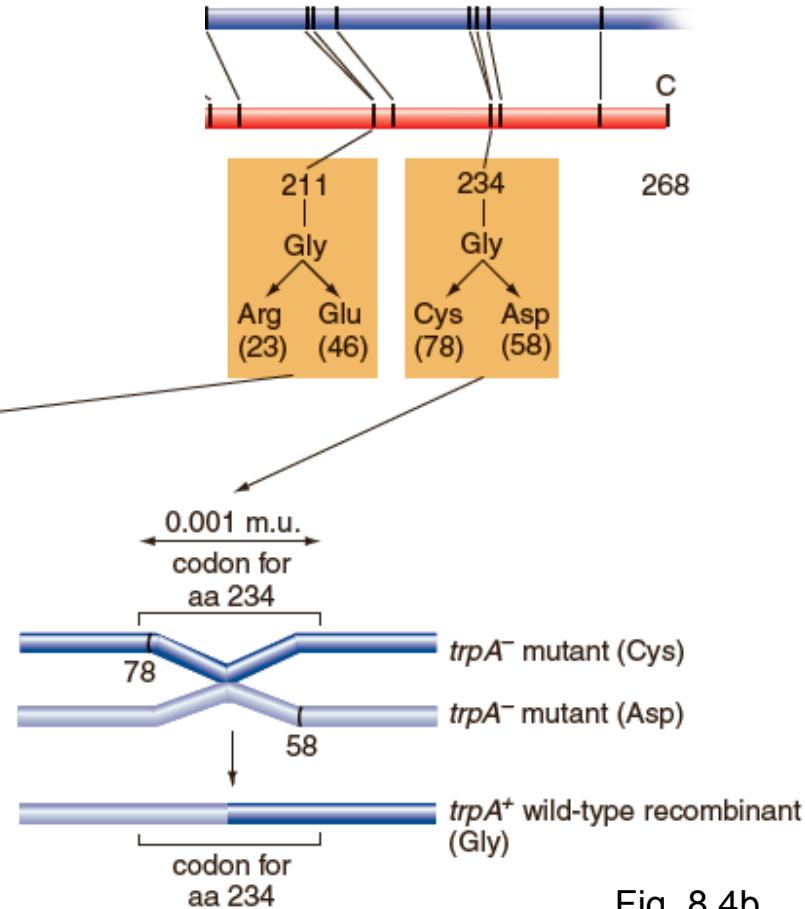
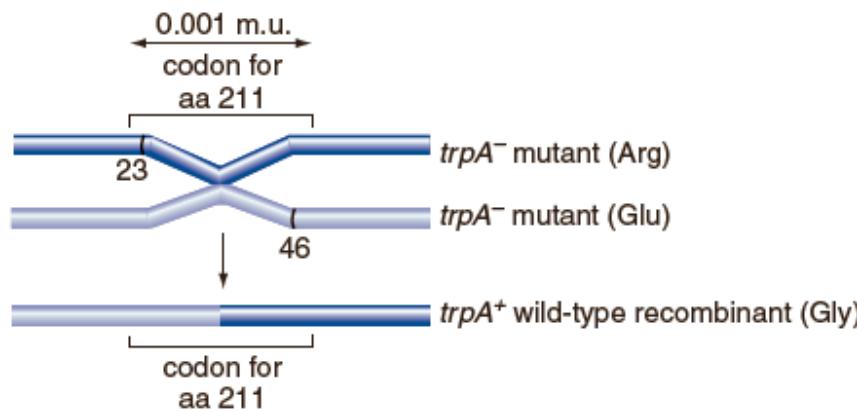


Fig. 8.4b

Studies of frameshift mutations showed that codons consist of three nucleotides

F. Crick and S. Brenner (1955)

Proflavin-induced mutations in bacteriophage T4 *rII*B gene

- Intercalates into DNA
- Causes insertions and deletions

2nd treatment with proflavin can create a 2nd mutation that restores wild-type function (revertant)

- Introngenic suppression)

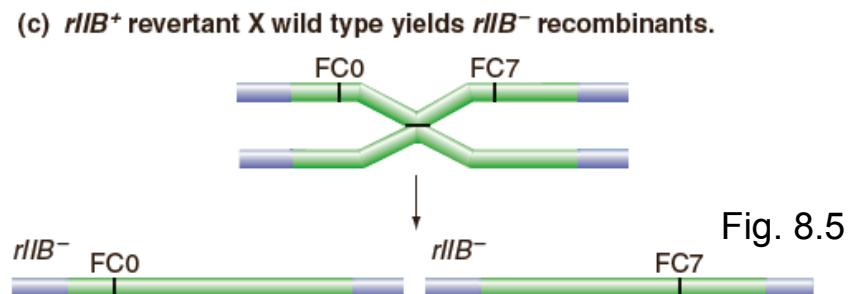
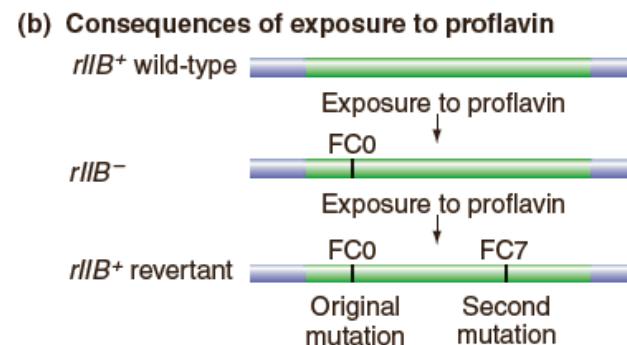
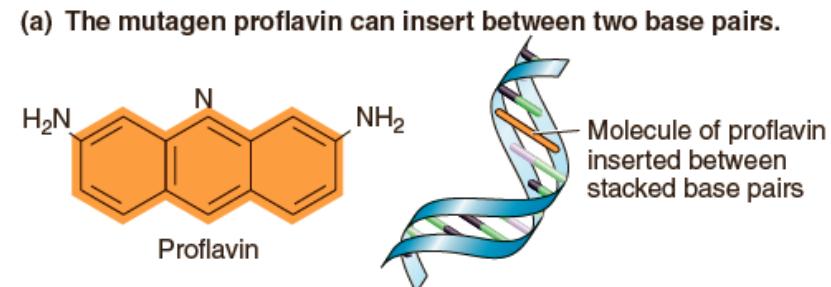


Fig. 8.5

Different sets of T4 *rII*B mutations generate either a mutant or a normal phenotype

Codons must be read in order from a fixed starting point

Starting point establishes a reading frame

Intragenic suppression occurs only when wild-type reading frame is restored

Proflavin-induced mutations (+) insertion (-) deletion	Phenotype
- or +	Mutant
-- or ++	Mutant
----- or ----- or +++++ or ++++++	Mutant
--+	Wild type
----- or ----- or +++ or ++++++	Wild type

Fig. 8.5d

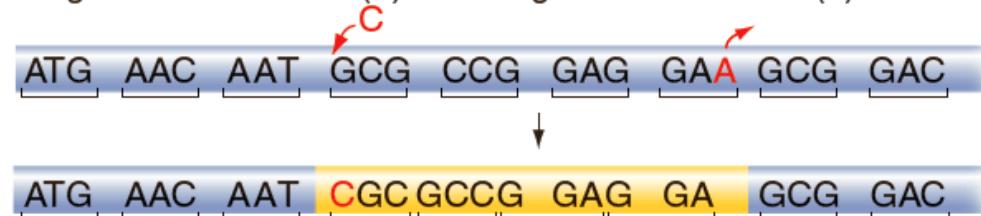
Codons consist of three nucleotides read in a defined reading frame

Counterbalancing of mutations (e.g. +1 and -1) can restore the reading frame

Intragenic suppression occurs when mutations involve multiples of three

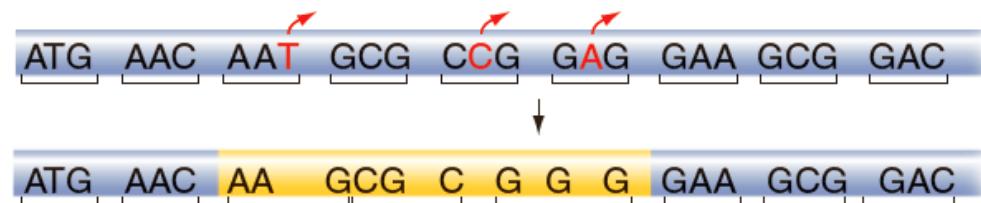
(a) Intragenic suppression: 2 mutations of opposite sign.

Single base insertion (+) and single base deletion (-)

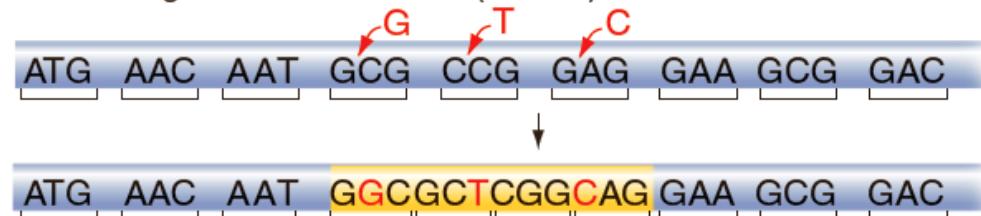


(b) Intragenic suppression: 3 mutations of the same sign.

Three single base deletions (---)



Three single base insertions (+++)



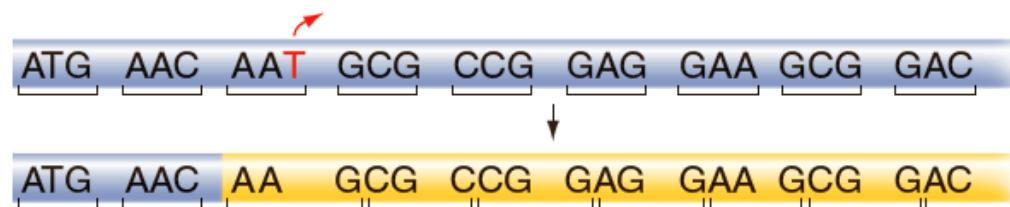
correct triplet
incorrect triplet

Fig. 8.6

Codons consist of three nucleotides read in a defined reading frame (cont)

Frameshift mutations alter the reading frame of codons after the point of insertion or deletion

Single base deletion (-)



correct triplet
incorrect triplet

Single base insertion (+)

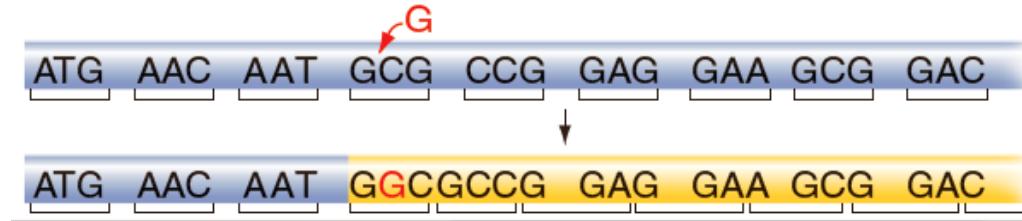


Fig. 8.6

Cracking the code: Which codons represent which amino acids?

Several technological breakthroughs in 1950s and 1960s

- Discovery of mRNA
- In vitro translation of synthetic mRNAs
 - Preparation of cellular extracts that allowed translation in a test tube
 - Developed techniques to synthesize artificial RNAs with known nucleotide sequence
 - Allowed synthesis of simple polypeptides

Cracking the code: Discovery of mRNA

1950s, studies in eukaryotic cells

Evidence that protein synthesis takes place in cytoplasm

- Deduced from radioactive tagging of amino acids
- Implies that there must be a molecular intermediate between genes in the nucleus and protein synthesis in the cytoplasm

Discovery of messenger RNAs (mRNAs), molecules for transporting genetic information

Using synthetic mRNAs and in vitro translation to crack the genetic code

1961 – Marshall Nirenberg and Heinrich Mathaei

Added artificial mRNAs to cell-free translation systems

(a) Poly-U mRNA encodes polyphenylalanine.

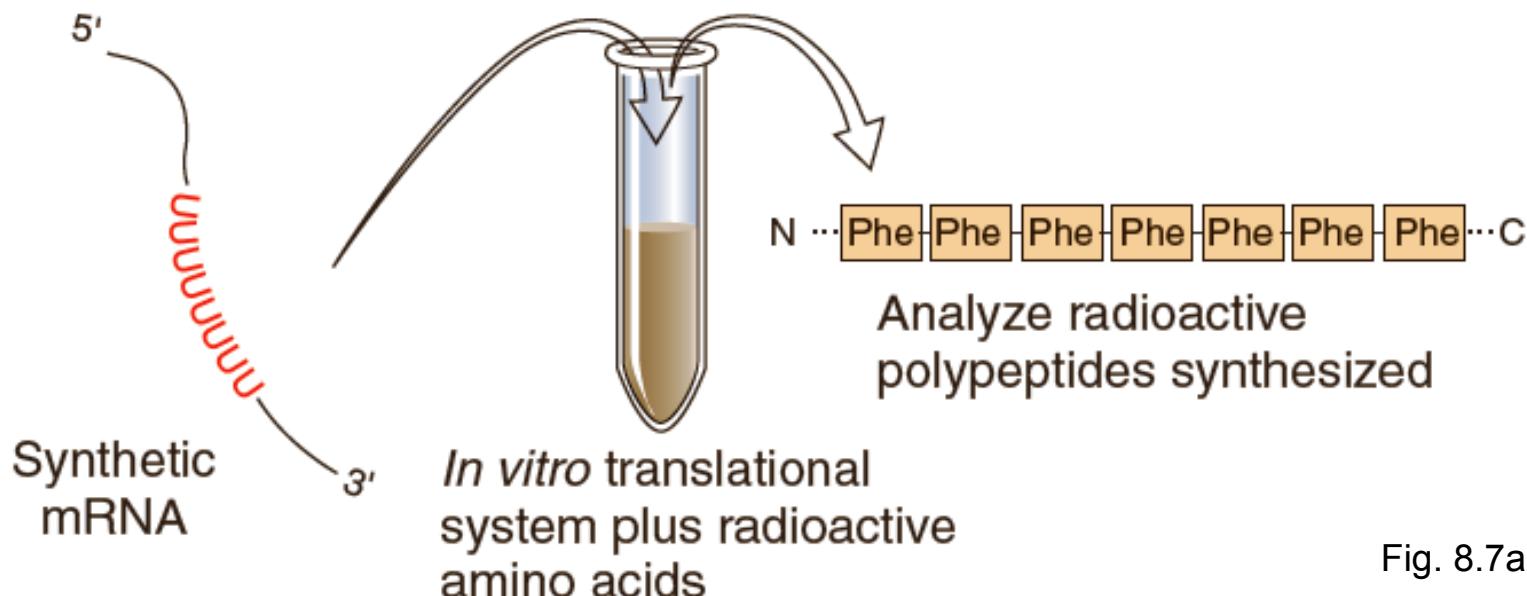


Fig. 8.7a

The coding possibilities of synthetic mRNAs

Simple polypeptides are encoded by simple polynucleotides

Fig. 8.7b

Synthetic mRNA	Polypeptides synthesized
	Polypeptides with one amino acid
poly-U UUUU ... poly-C CCCC ... poly-A AAAA ... poly-G GGGG ...	Phe-Phe-Phe ... Pro-Pro-Pro ... Lys-Lys-Lys ... Gly-Gly-Gly ...
Repeating dinucleotides	Polypeptides with alternating amino acids
poly-UC UCUC ... poly-AG AGAG ... poly-UG UGUG ... poly-AC ACAC ...	Ser-Leu-Ser-Leu ... Arg-Glu-Arg-Glu ... Cys-Val-Cys-Val ... Thr-His-Thr-His ...
Repeating trinucleotides	Three polypeptides each with one amino acid
poly-UUC UUCUUUCUUC ... poly-AAG AAGAAAGAAG ... poly-UUG UUGUUGUUG ... poly-UAC UACUACUAC ...	Phe-Phe.... and Ser-Ser.... and Leu-Leu... Lys-Lys.... and Arg-Arg.... and Glu-Glu.... Leu-Leu.... and Cys-Cys.... and Val-Val.... Tyr-Tyr.... and Thr-Thr.... and Leu-Leu....
Repeating tetranucleotides	Polypeptides with repeating units of four amino acids
poly-UAUC UAUCUAUC ... poly-UUAC UUACUUAC ... poly-GUAA GUAAGUAA ... poly-GAUA GAUAGAUA ...	Tyr-Leu-Ser-Ile-Tyr-Leu-Ser-Ile... Leu-Leu-Thr-Tyr-Leu-Leu-Thr-Tyr... none none

Cracking the genetic code with mini-mRNAs

Nirenberg and Leder
(1965)

Resolved ambiguities
in genetic code

In vitro translation
with trinucleotide
synthetic mRNAs and
tRNAs charged with a
radioactive amino acid

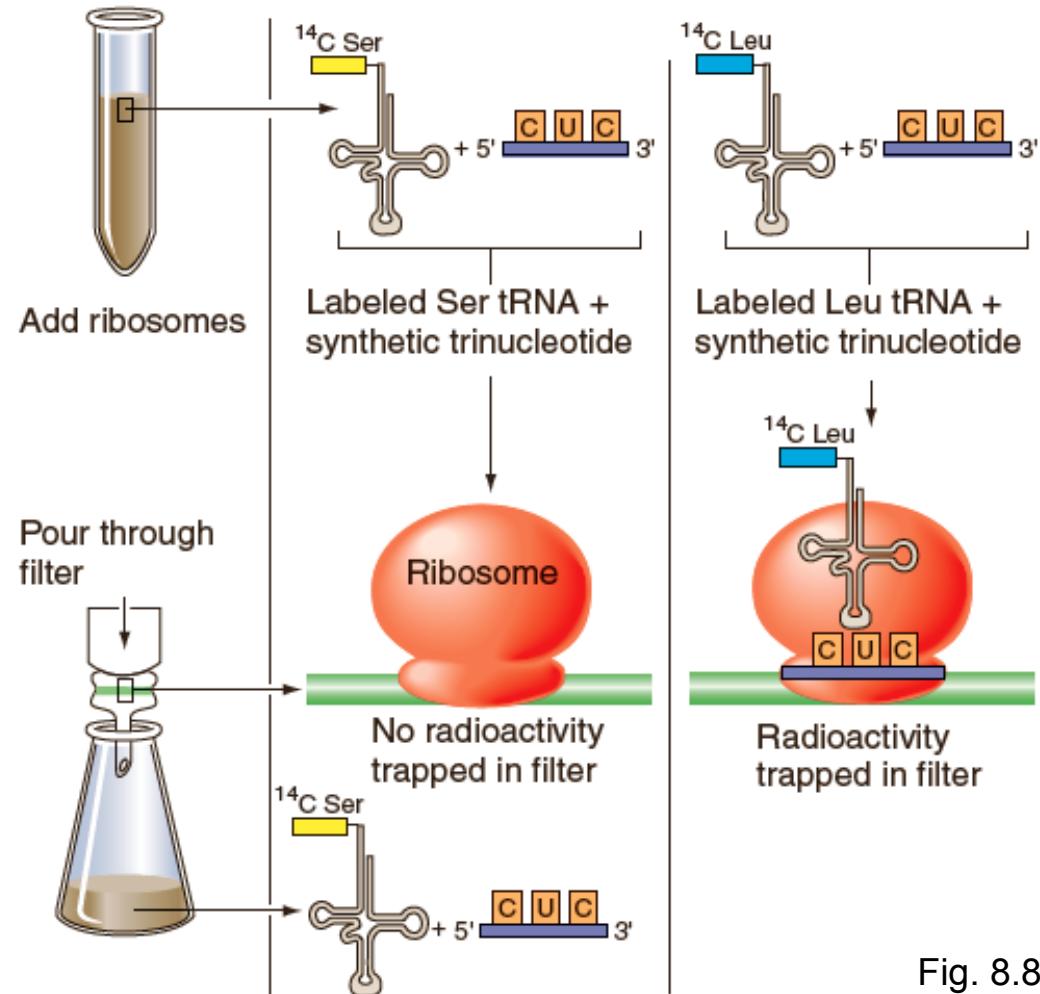


Fig. 8.8

Correlation of polarities in DNA, mRNA, and polypeptide

Template strand of DNA is complementary to mRNA and to the RNA-like strand of DNA

5'-to-3' in the mRNA corresponds to N-to-C-terminus in the polypeptide

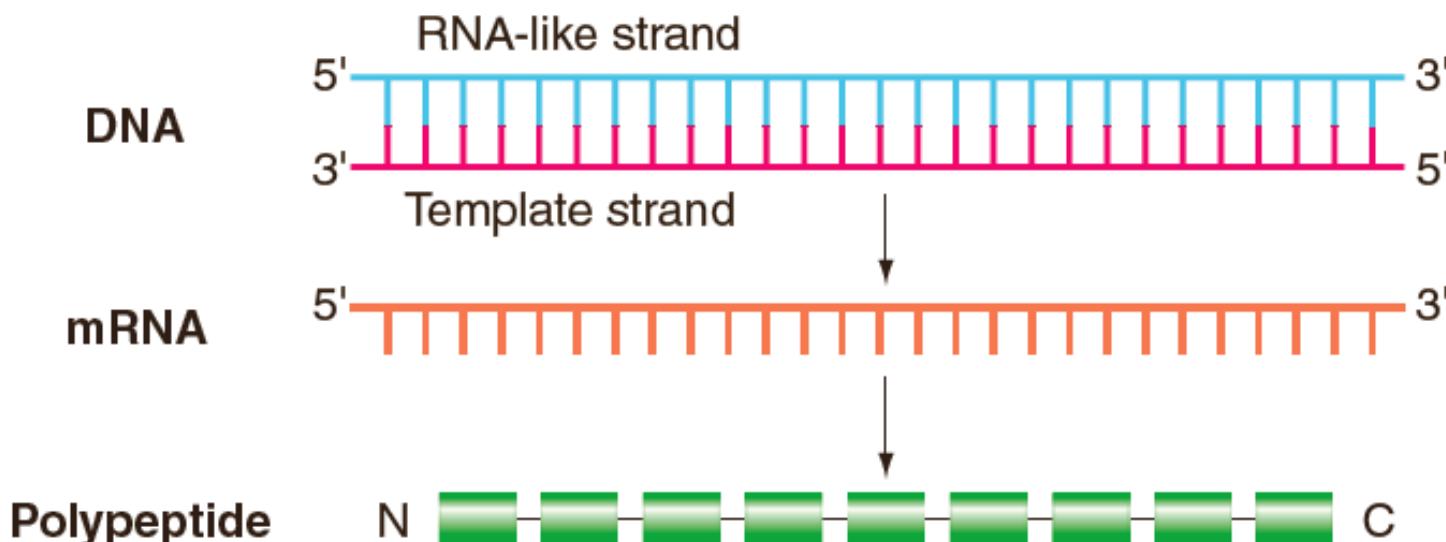


Fig. 8.9

Summary of the genetic code

Genetic code has triplet codons

Codons are nonoverlapping

Three nonsense codons don't encode an amino acid; UAA (ocher), UAG (amber) and UGA (opal)

Genetic code is degenerate

Reading frame is established from a fixed starting point – codon for translation initiation is AUG

mRNAs and polypeptides have corresponding polarities

Mutations can be created in three ways; frameshift, missense, and nonsense

Experimental verification of the genetic code

Yanofsky: Single-base substitutions can explain the altered amino acids in *trp*⁻ and *trp*⁺ revertants

**Missense mutations
are single nucleotide
substitutions and
conform to the code**

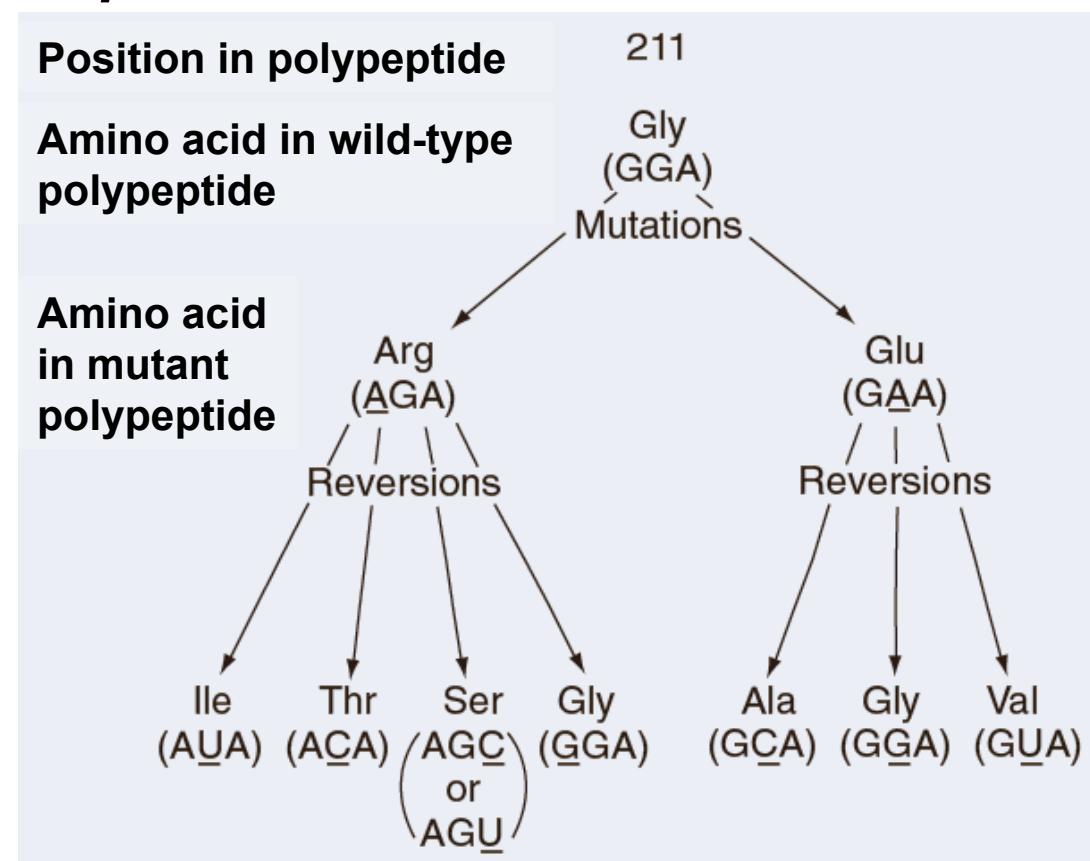


Fig. 8.10a

Experimental verification of the genetic code (cont)

Yanofsky: Amino acid alterations that explain intragenic suppression of proflavin-induced frame-shift mutations

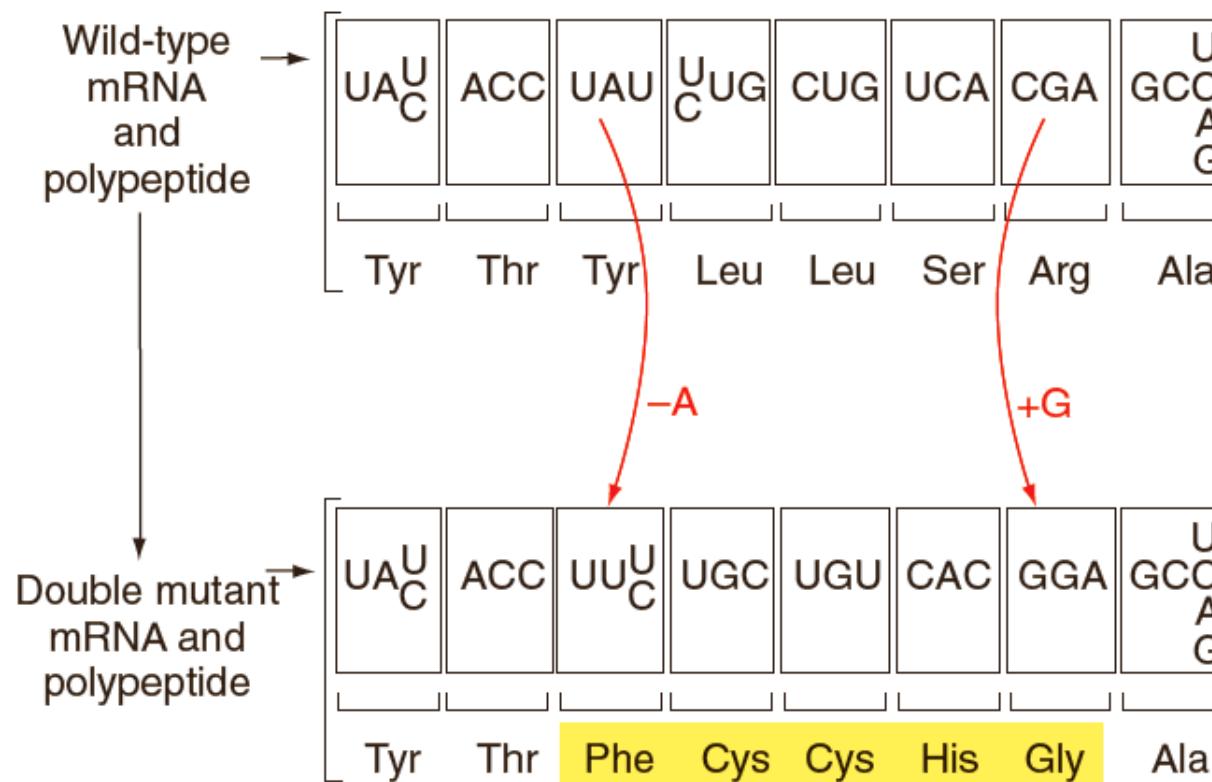


Fig. 8.10b

Genetic code is almost, but not quite, universal

Virtually all cells alive now use the same basic genetic code

- **In vitro translational systems from one organism can use mRNA from another organism to generate protein**
- **Comparisons of DNA and protein sequence reveal perfect correspondence between codons and amino acids among all organisms**

Genetic code must have evolved early in history of life

Exceptional genetic codes found in ciliates and mitochondria

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Transcription: From DNA to RNA

RNA polymerase catalyzes transcription

Promoters are DNA sequences that provide the signal to RNA polymerase for starting transcription

RNA polymerase adds nucleotides in 5'-to-3' direction

- Formation of phosphodiester bonds using ribonucleotide triphosphates (ATP, CTP, GTP, and UTP)
- Hydrolysis of bonds in NTPs provides energy for transcription

Terminators are RNA sequences that provide the signal to RNA polymerase for stopping transcription

Transcription in bacterial cells

Initiation: The beginning of transcription

RNA polymerase binds to promoter sequence located near beginning of gene

- Sigma (σ) factor binds to RNA polymerase (\rightarrow holoenzyme)
- Region of DNA is unwound to form open promoter complex
- Phosphodiester bonds formed between first two nucleotides

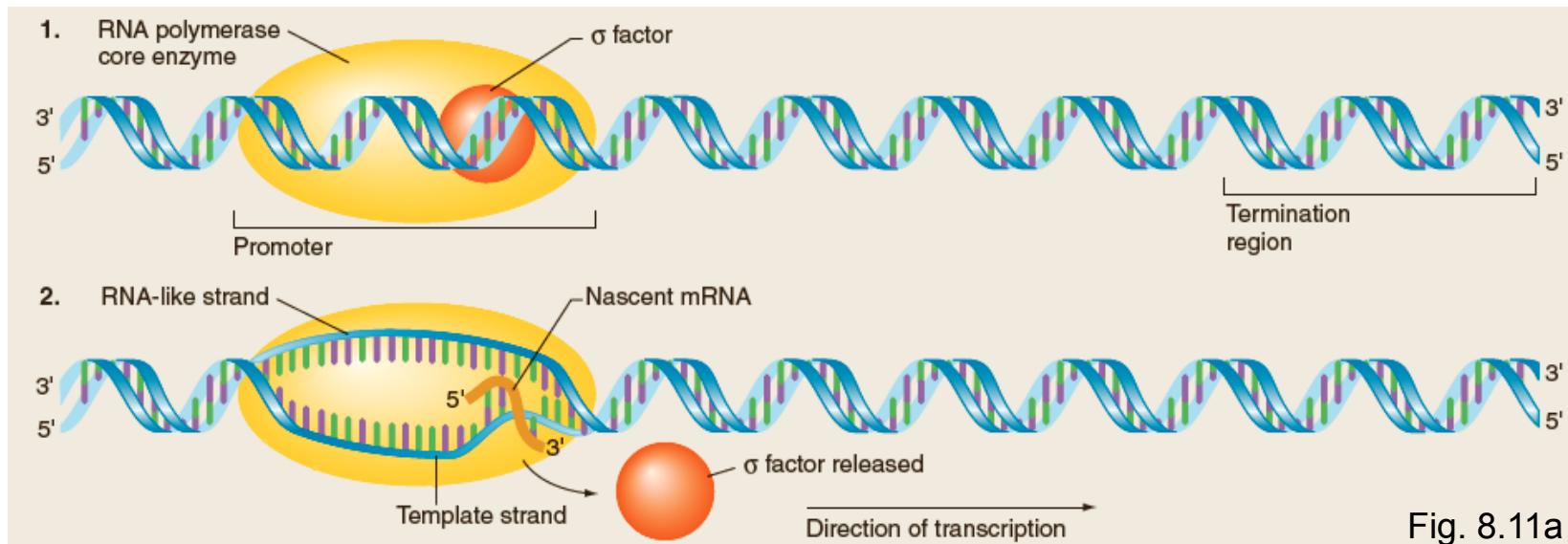


Fig. 8.11a

Transcription in bacterial cells

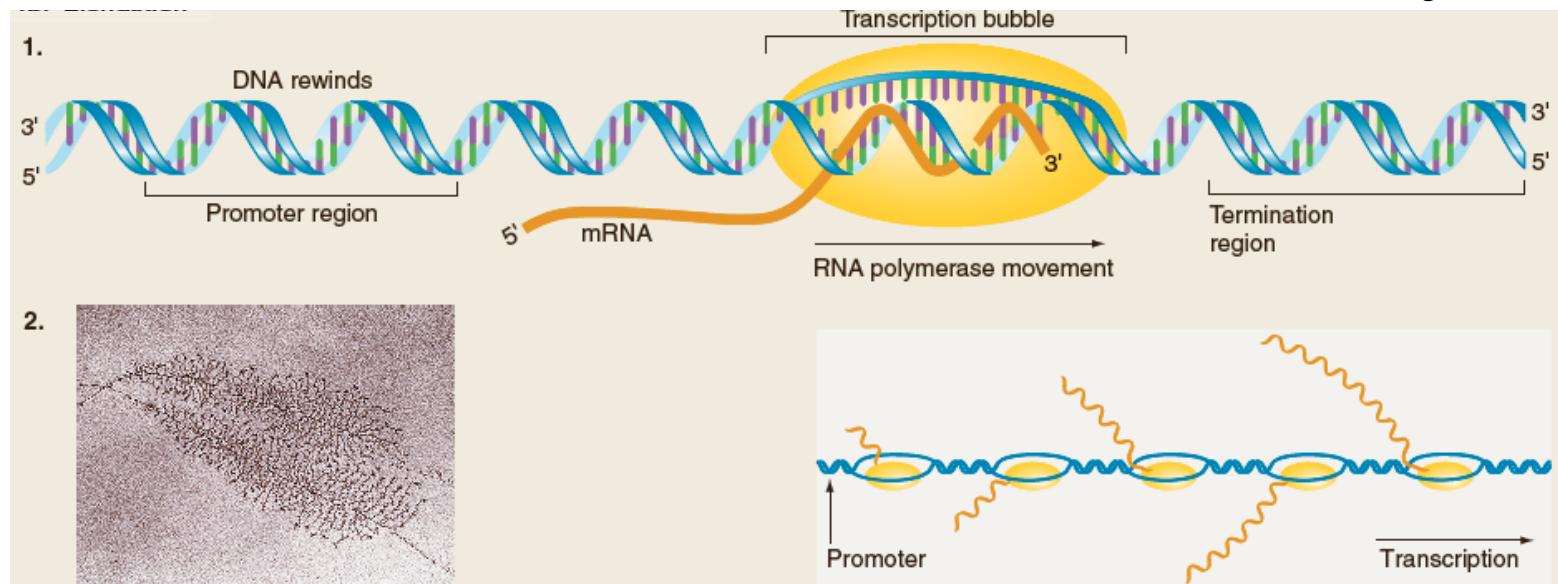
Elongation: An RNA copy of the gene

σ factor separates from RNA polymerase (\rightarrow core enzyme)

Core RNA polymerase loses affinity for promoter, moves in 3'-to-5' direction on template strand

Within transcription bubble, NTPs added to 3' end of nascent mRNA

Fig. 8.11b



Transcription in bacterial cells

Termination: The end of transcription

Terminators are RNA sequences that signal the end of transcription

- Two kinds of terminators in bacteria: **extrinsic** (require rho factor) and **intrinsic** (don't require additional factors)
- Usually form hairpin loops (intramolecular H-bonding)

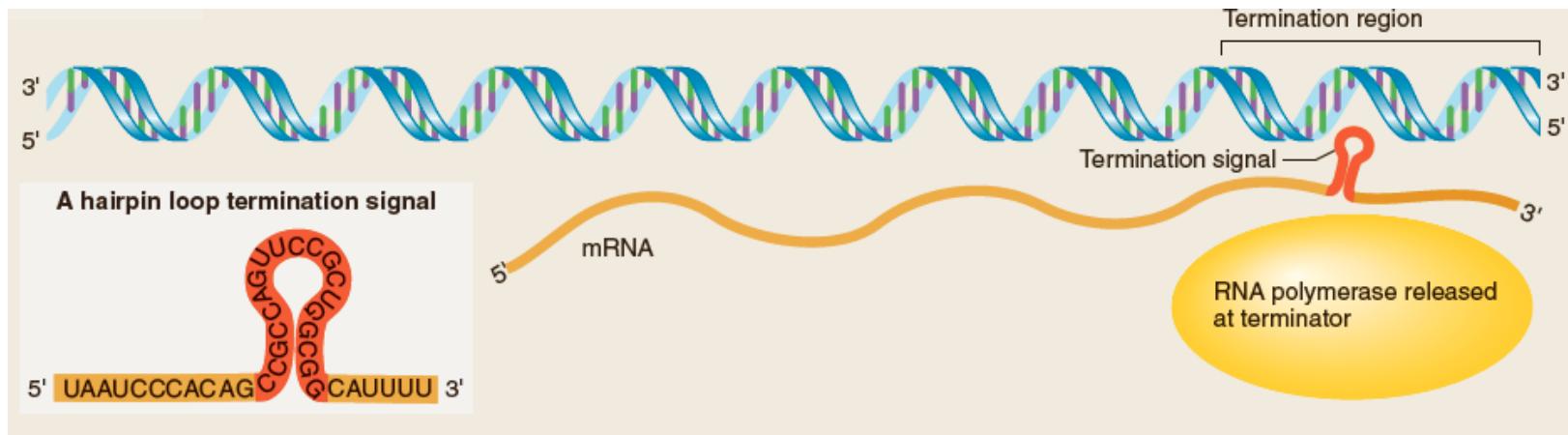


Fig. 8.11c

The product of transcription is a single-stranded primary transcript

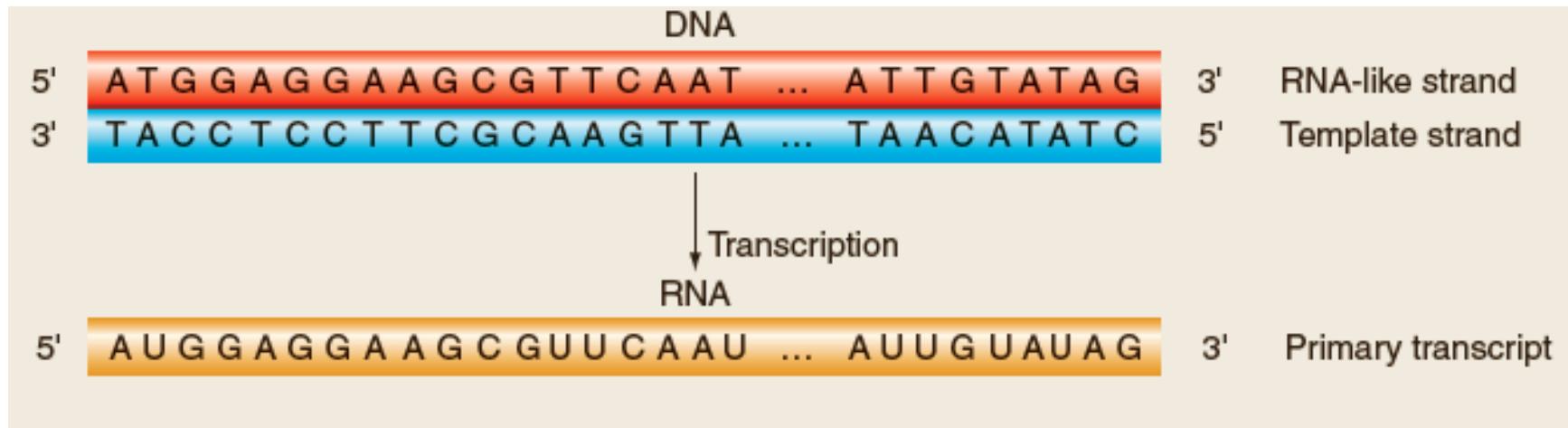
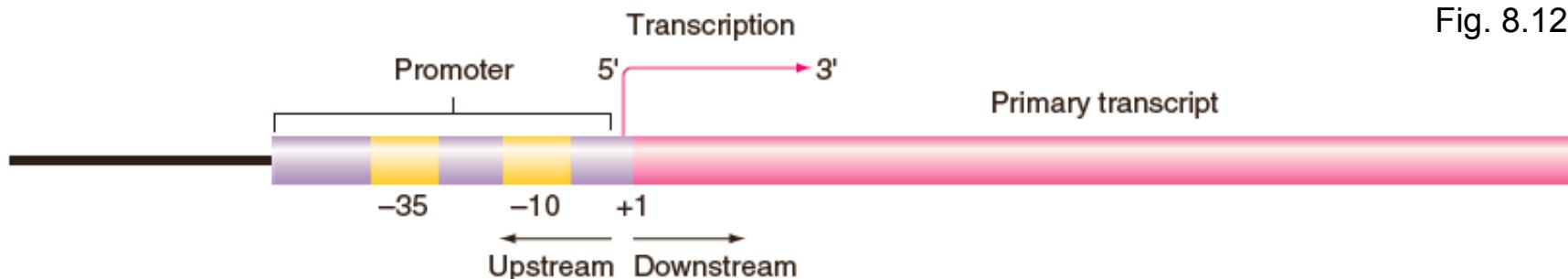


Fig. 8.11d

The promoters of 10 different bacterial genes

Most promoters are upstream to the transcription start point

RNA polymerase makes strong contacts at -10 and -35



Strong E. coli promoters

Gene	Sequence
rrn X1	ATGCATTTTCCGCTTGTCTTCCTGA • • GCCGACTCCCTATAATGCGCCTCCATCGACACGGCGGAT
rrn (DXE) ₂	CCTGAAATTCAAGGGTTGACTCTGAAA • • GAGGAAAGCGTAATATAACGCCACCTCGCGACAGTGAGC
rrn A1	TTTTAAATTCCCTTTGTCAAGGCCGG • • AATAACTCCCTATAATGCGCCACCACTGACACGGAACAA
rrn A2	GCAAAATAAAAATGCTTGACTCTGTAG • • CGGGAAAGGCGTATTATGCACACCCCGCGCGCTGAGAA
λ PR	TAACACCGTGC GTGTTGACTATTTA • CCTCTGGCGGTGATAATGG • • TTGCATGTACTAAAGGAGGT
λ PL	TATCTCTGGCGGTGTTGACATAATA • CCACTGGCGGTGATACTGA • • GCACATCA GCAGGACGCAC
T7 A3	GTGAAACAAAACGGTTGACAACATGA • AGTAAACACGGTACGATGT • ACCACATGAAACGACAGTGA
T7 A1	TATCAAAAAGAGTATTGACTTAAAGT • CTAACCTATAGGATACTT A • CAGCCATCGAGAGGGACACG
T7 A2	ACGAAAAACAGGTATTGACAACATGAAGTAACATGCAGTAAGATA C • AAATCGCTAGGTAAACACTAG
fd VIII	GATACAAATCTCCGTTGTACTTTGTT • • TCGCGCTTGGTATAATCG • CTGGCGTCAAAGATGAGTG
-35 region	
-10 region	
+1	
Consensus	TTGACAT ————— 15 – 17 bp ————— TATAAT ————— 5' ————— 3' Primary transcript

Structure of the methylated cap at the 5' end of eukaryotic mRNAs

Capping enzyme adds a "backward" G to the 1st nucleotide of a primary transcript

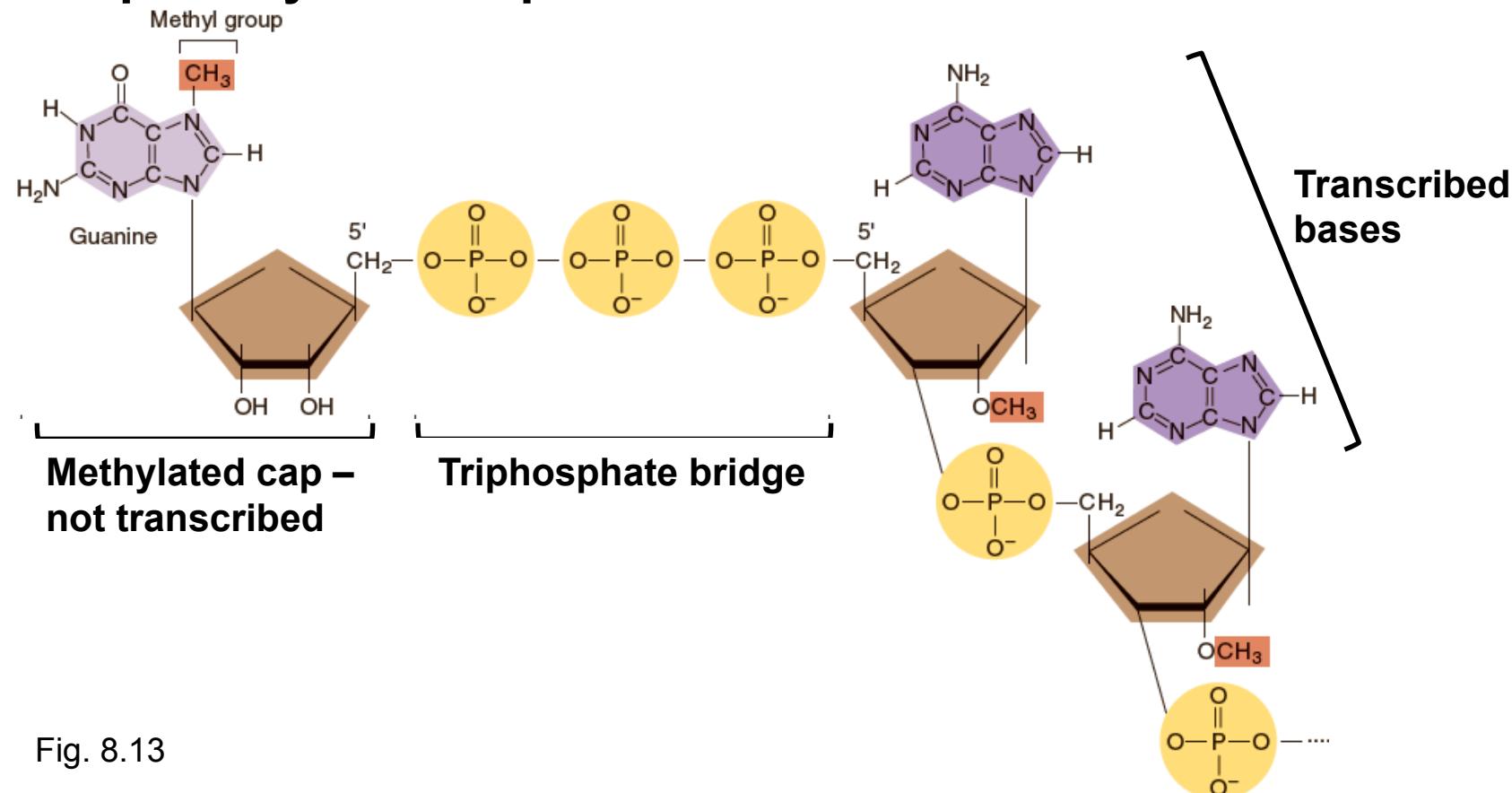


Fig. 8.13

Processing adds a tail to the 3' end of eukaryotic mRNAs

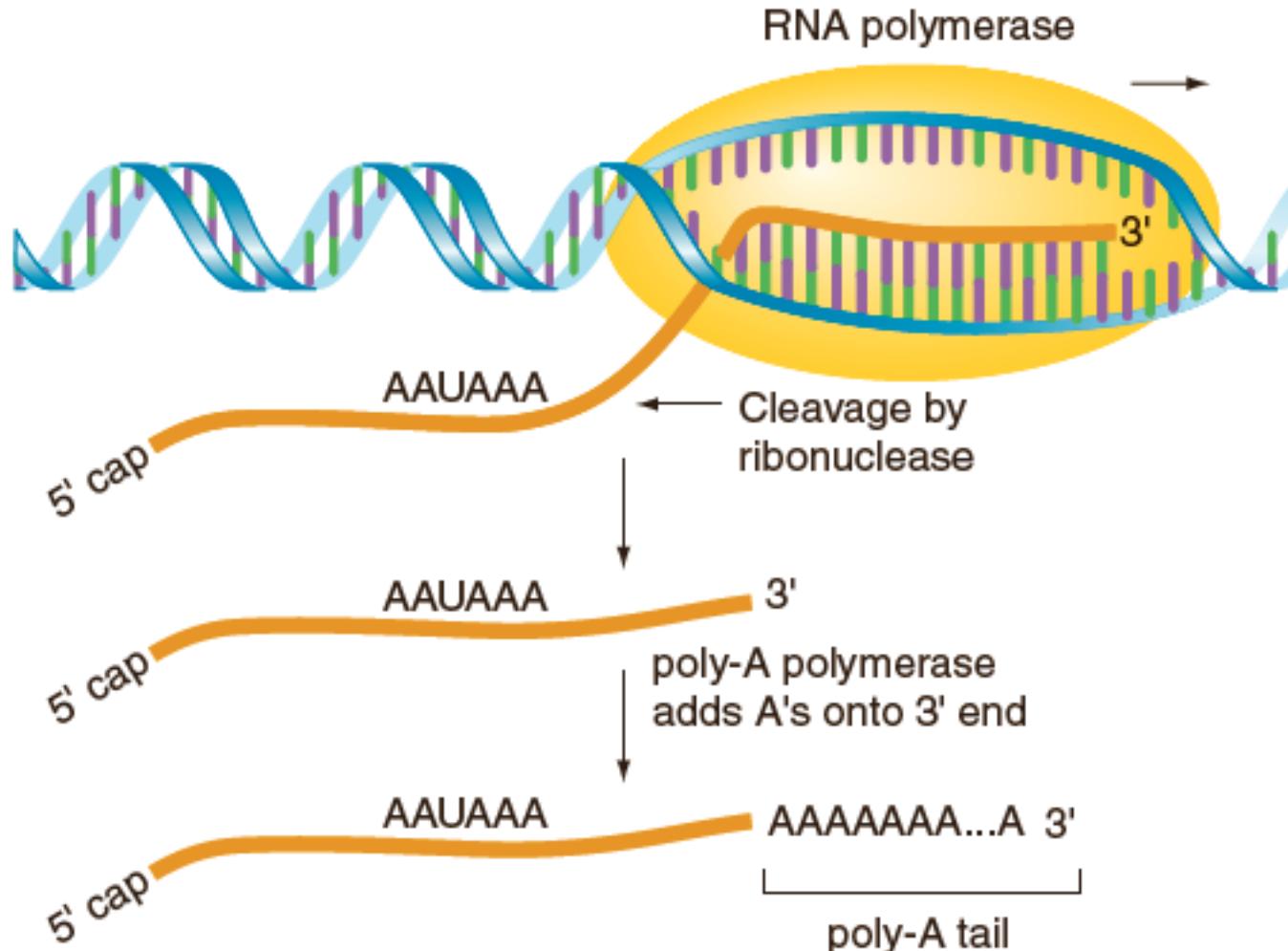


Fig. 8.14

RNA splicing removes introns

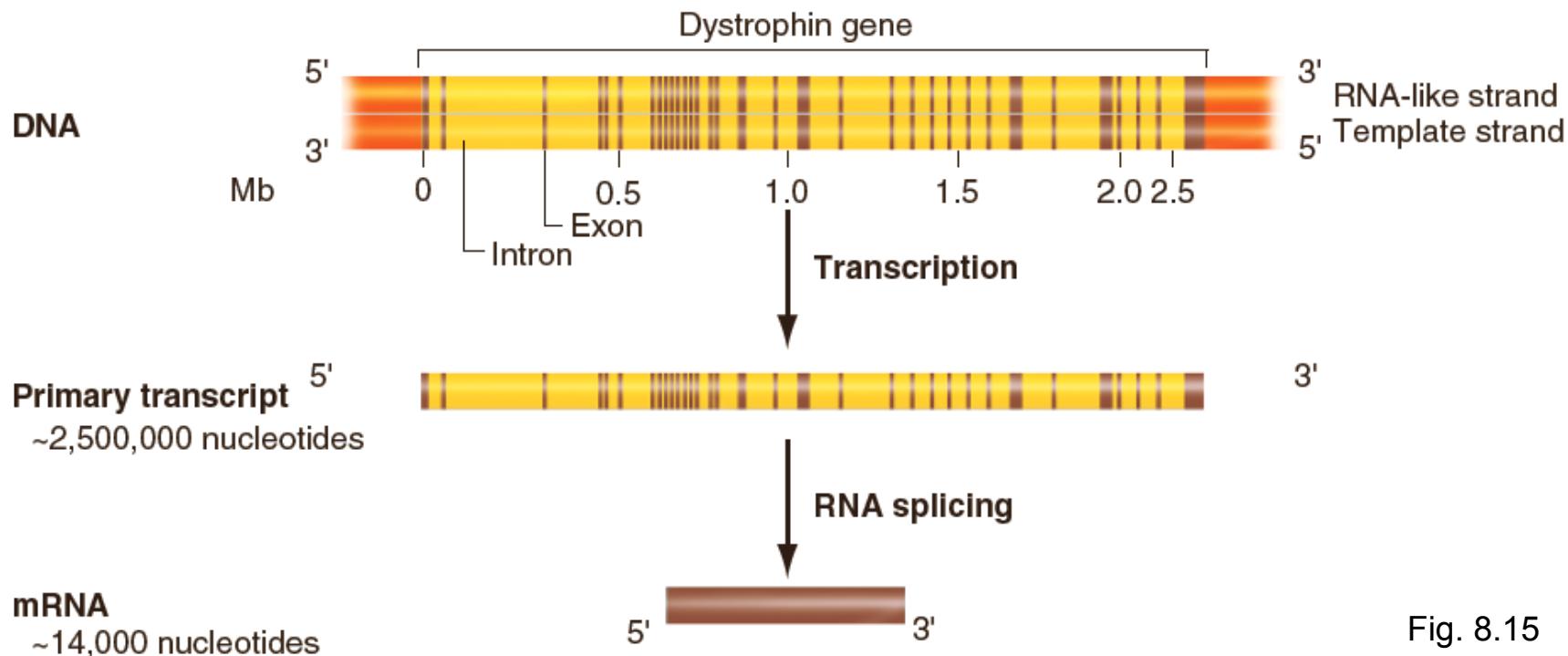
Exons – sequences found in a gene's DNA and mature mRNA (expressed regions)

Introns – sequences found in DNA but not in mRNA (intervening regions)

Some eukaryotic genes have many introns

The human dystrophin gene: An extreme example of RNA splicing

Splicing removes introns from a primary transcript



RNA processing splices out introns and joins adjacent exons

Short sequences in the primary transcript dictate where splicing occurs

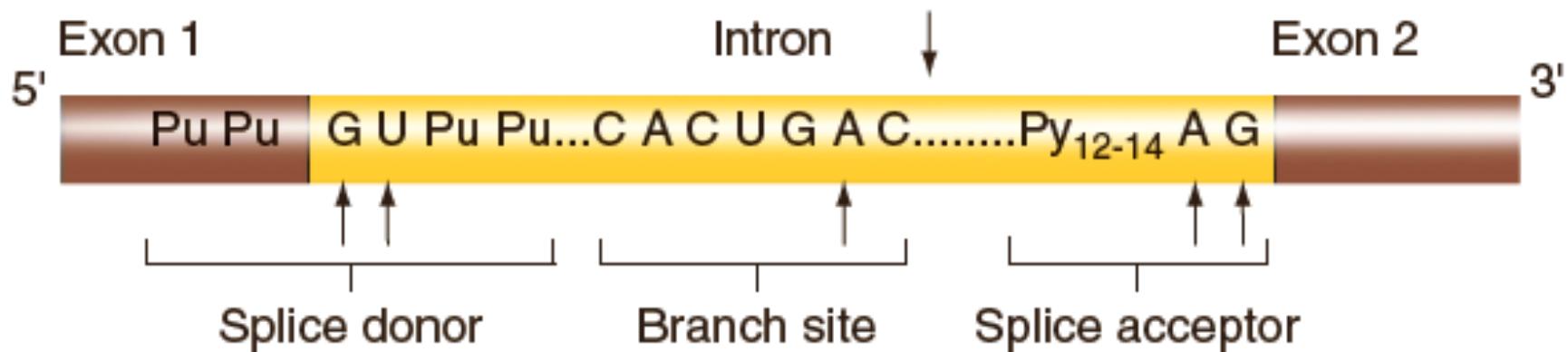


Fig. 8.16a

RNA processing splices out introns and joins adjacent exons (cont)

Two sequential cuts remove an intron

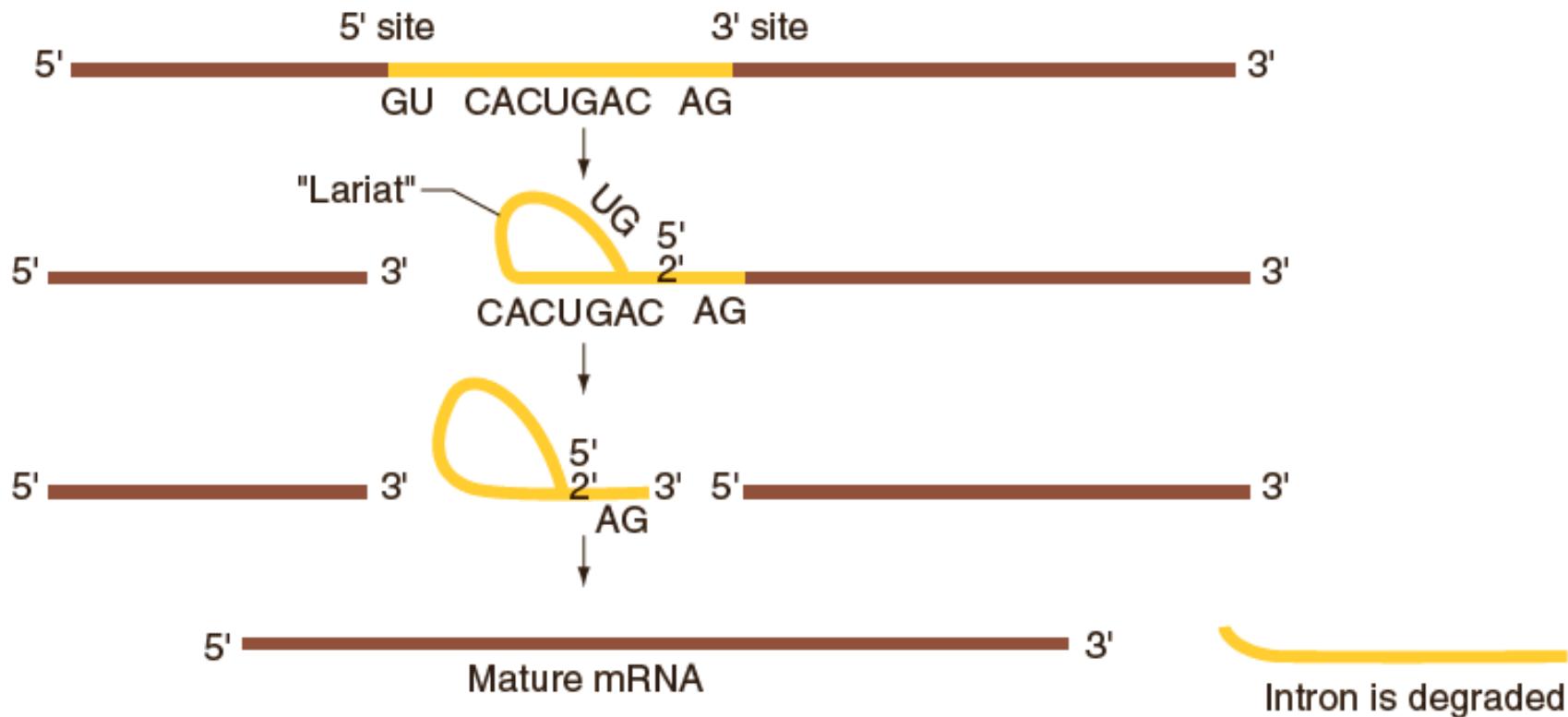


Fig. 8.16b

Splicing is catalyzed by the spliceosome

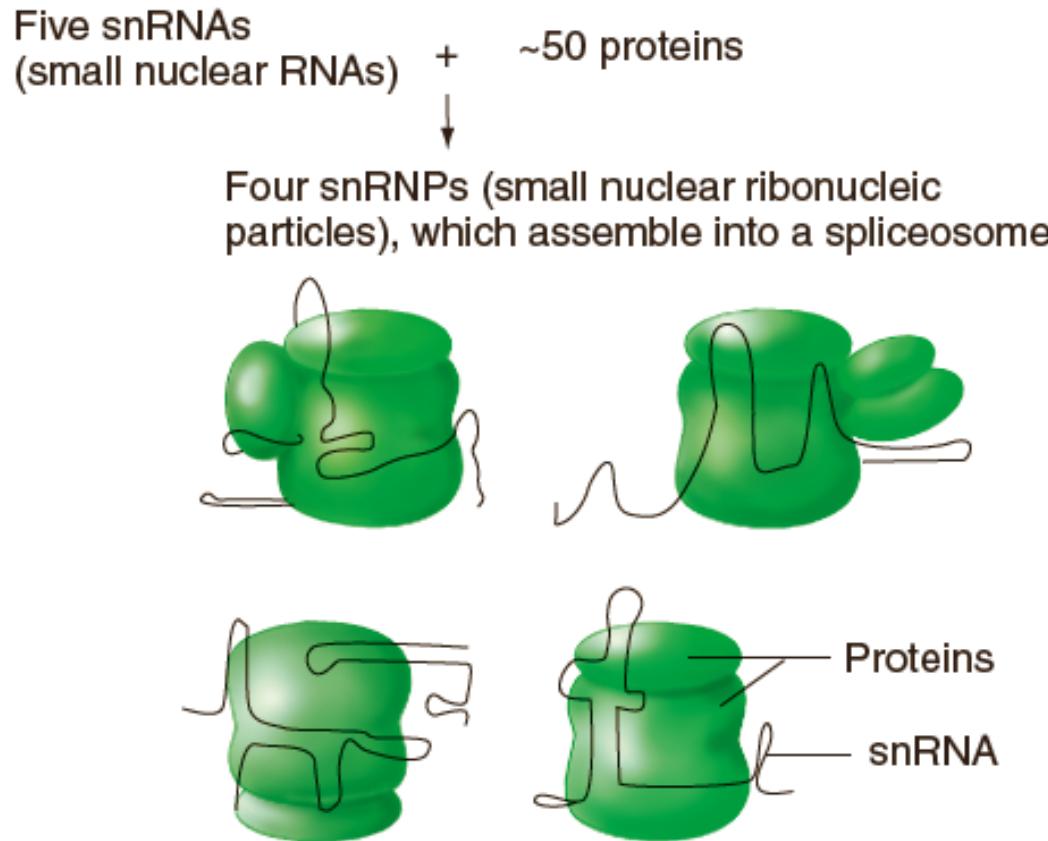


Fig. 8.17

Alternative splicing can produce two different mRNAs from the same gene

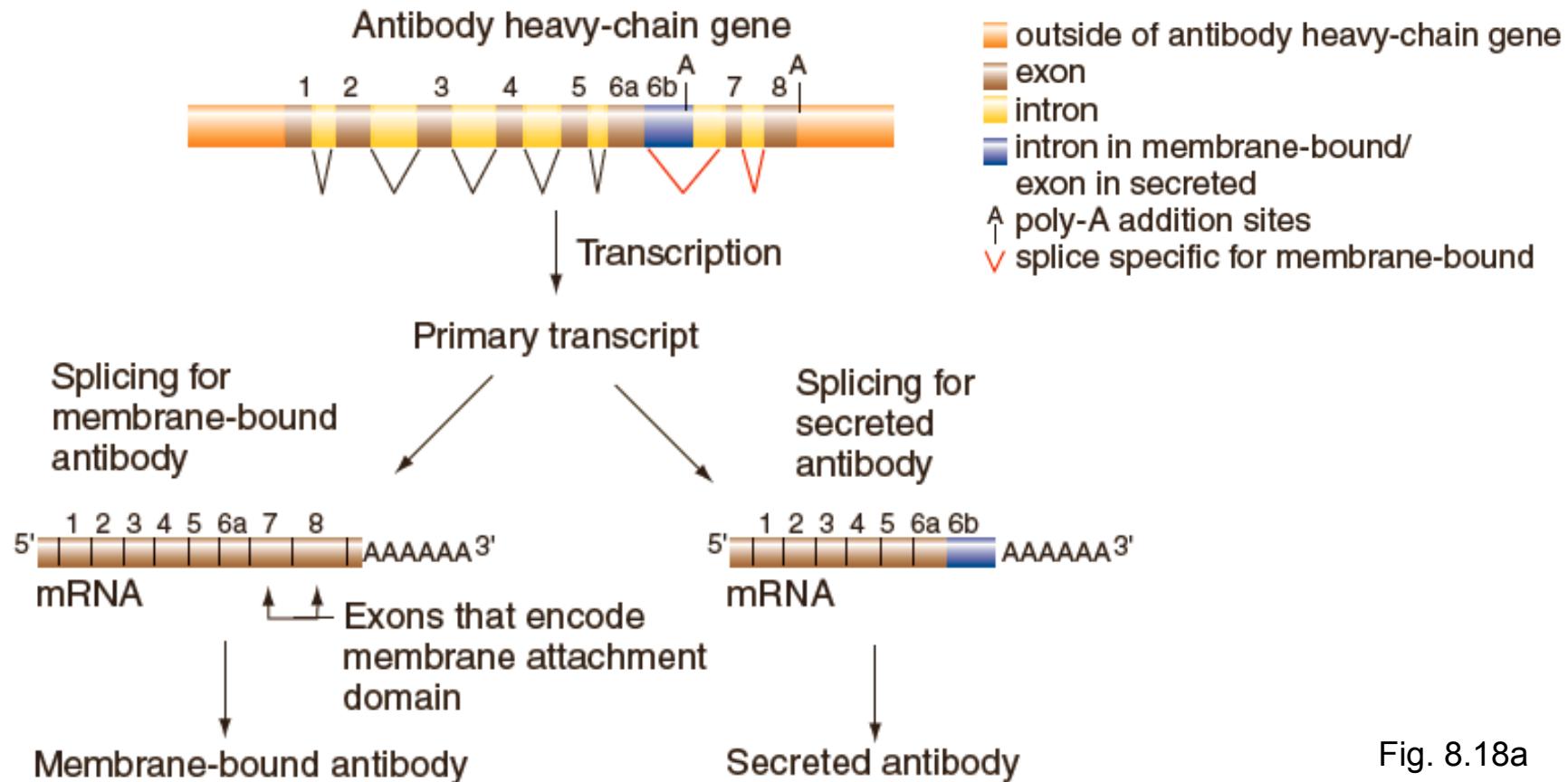


Fig. 8.18a

Trans-splicing combines exons from different genes

Occurs in *C. elegans* and a few other organisms

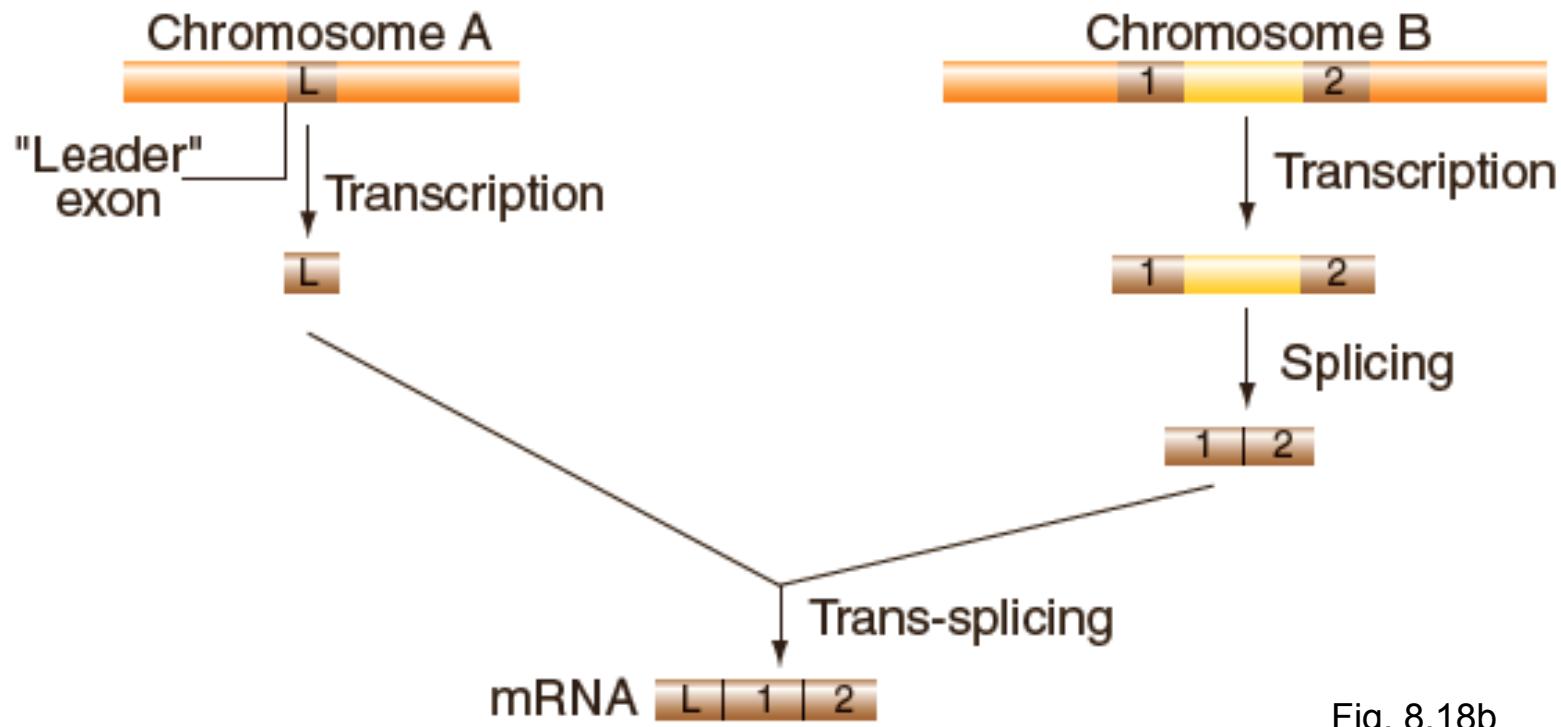


Fig. 8.18b

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Translation: From mRNA to protein

Transfer RNAs (tRNAs) mediate translation of mRNA codons to amino acids

Translation takes place on **ribosomes that coordinate movement of tRNAs carrying specific amino acids**

tRNAs are short single-stranded RNAs of 74 – 95 nt

- Each tRNA has an **anticodon** that is complementary to an mRNA codon
- A specific tRNA is covalently coupled to a specific amino acid (**charged tRNA**)
- Base pairing between an mRNA codon and an anticodon of a charged tRNA directs amino acid incorporation into a growing polypeptide

Some tRNAs contain modified bases

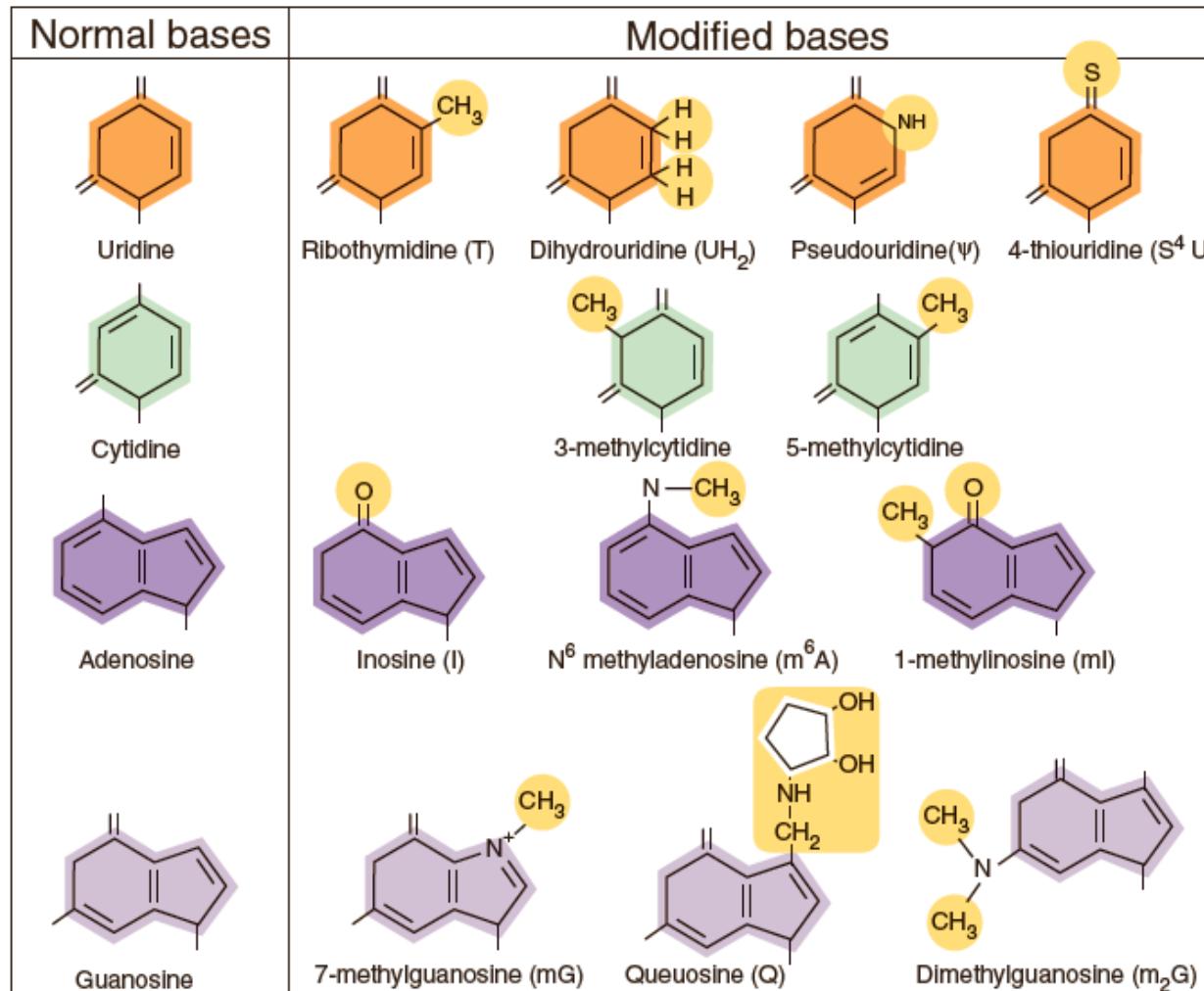


Fig. 8.19a

Three levels of tRNA structure

Nucleotide sequence is the primary structure

Secondary structure (cloverleaf shape) is formed because of short complementary sequences within the tRNA

Tertiary structure (L shape) is formed by 3-dimensional folding

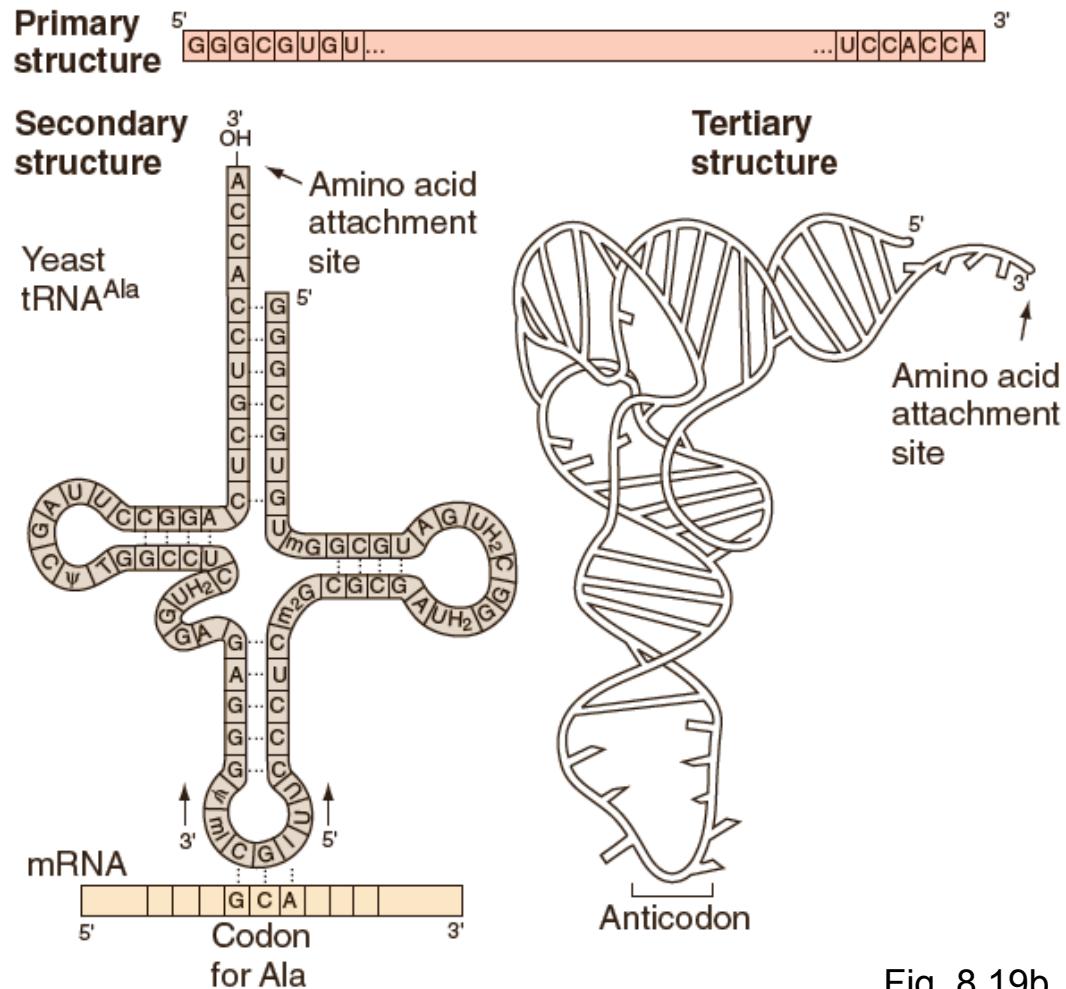


Fig. 8.19b

Aminoacyl-tRNA synthetases catalyze attachment of amino acids to specific tRNAs

Each **aminoacyl-tRNA synthetase** recognizes a specific amino acid and the structural features of its corresponding tRNA

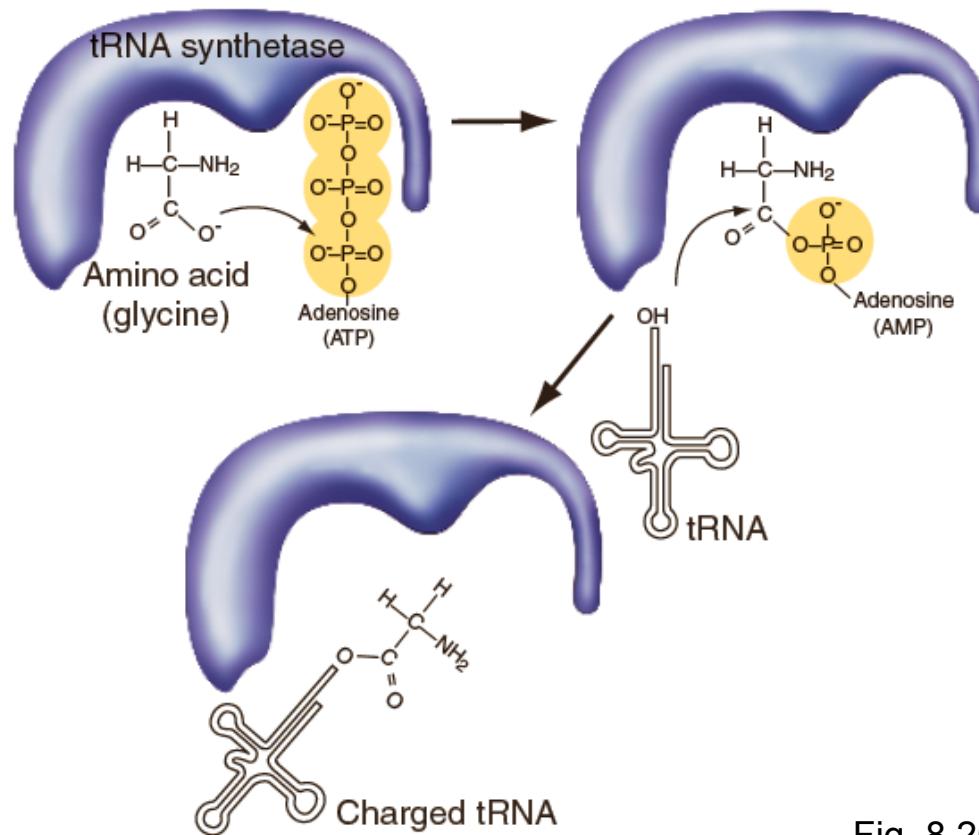
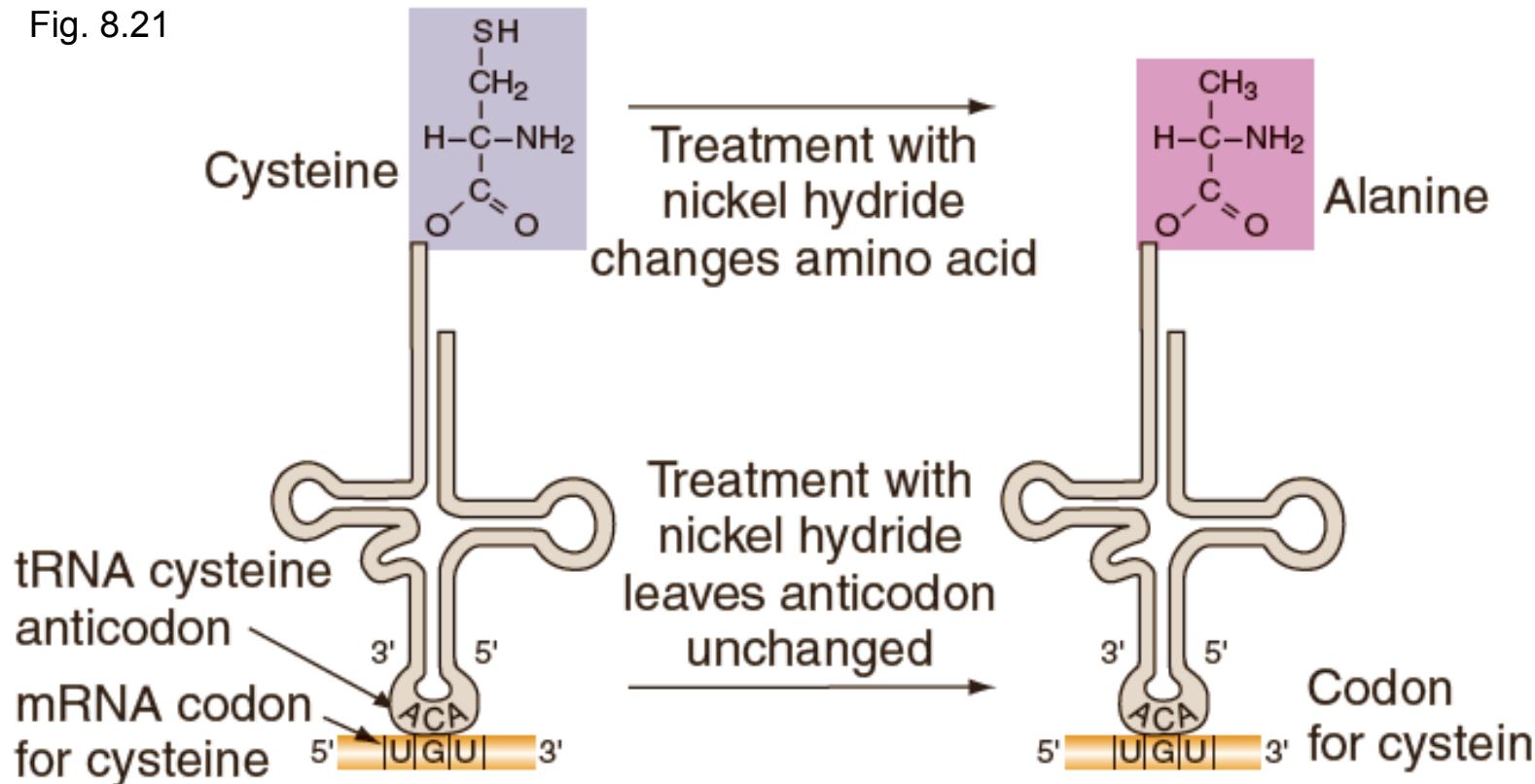


Fig. 8.20

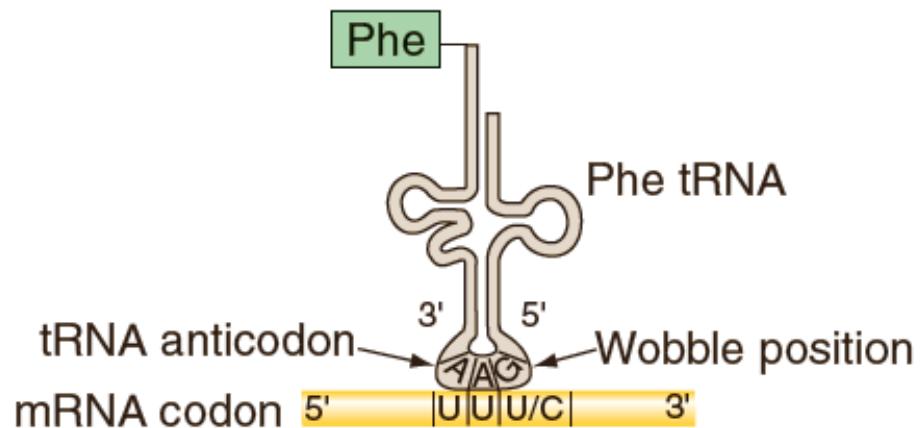
Base pairing between an mRNA codon and a tRNA anticodon determines which amino acid is added to a growing polypeptide

Fig. 8.21



Wobble: Some tRNAs recognize more than one codon for the amino acid they carry

(a)



(b)

Wobble Rules		
5' end of anticodon	can pair with	3' end of codon
G		U or C
C		G
A		U
U		A or G
I		U,C, or A

Fig. 8.22

A ribosome has two subunits composed of RNA and protein

Complete Ribosomes	Subunits	Nucleotides	Proteins
Prokaryotic 	 50S	 23S rRNA 3000 nucleotides 5S rRNA 120 nucleotides	31
	 30S	 16S rRNA 1700 nucleotides	21
Eukaryotic 	 60S	 28S rRNA 5000 nucleotides 5.8S rRNA 160 nucleotides 5S rRNA 120 nucleotides	~ 45
	 40S	 18S rRNA 2000 nucleotides	~ 33

Fig. 8.23a

Mechanism of translation

Initiation stage - start codon is AUG at 5' end of mRNA

- In bacteria, initiator tRNA has formylated methionine (fMet)

Elongation stage - amino acids are added to growing polypeptide

- Ribosomes move in 5'-to-3' direction along mRNA
- 2-15 amino acids added to C terminus per second

Termination stage - polypeptide synthesis stops at the 3' end of the reading frame

- Recognition of nonsense codons
- Polypeptide synthesis halted by release factors
- Release of ribosomes, polypeptide, and mRNA

Different parts of a ribosome have different functions

Small subunit binds to mRNA

Large subunit has peptidyl transferase activity

Three distinct tRNA binding areas – E, P, and A sites

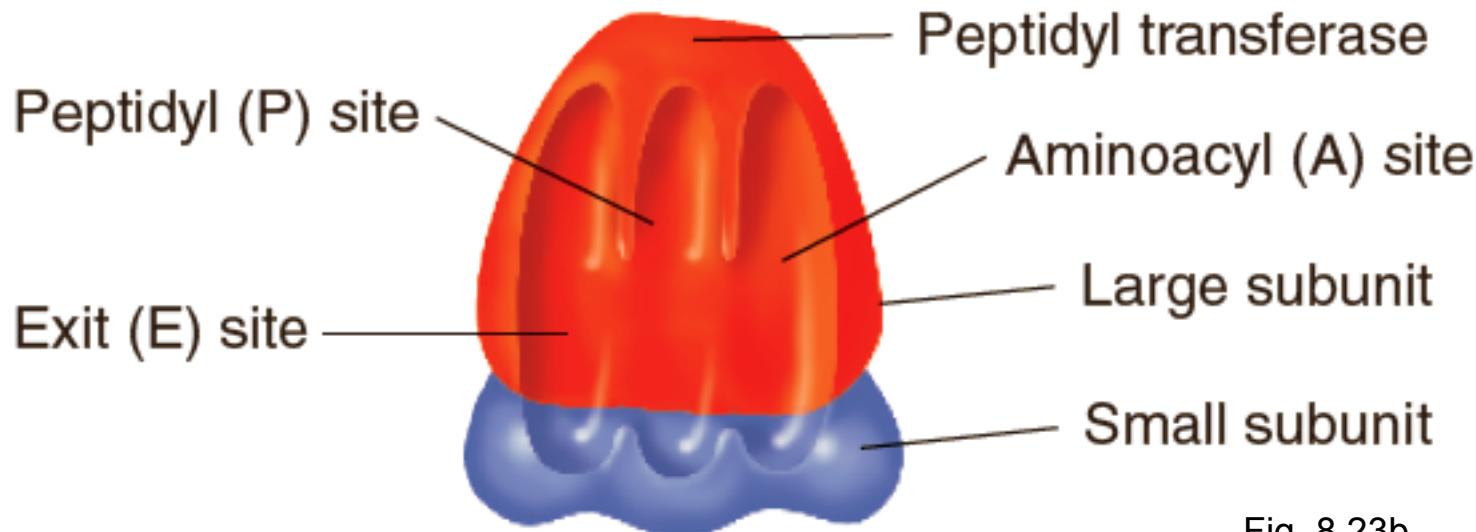


Fig. 8.23b

Translation of mRNAs on ribosomes: Initiation phase in prokaryotes

Ribosome binding site consists of a Shine-Dalgarno sequence and an AUG

Three sequential steps: small ribosomal subunit binds first, fMet-tRNA positioned in P site, large subunit binds

Initiation factors (not shown) play a transient role

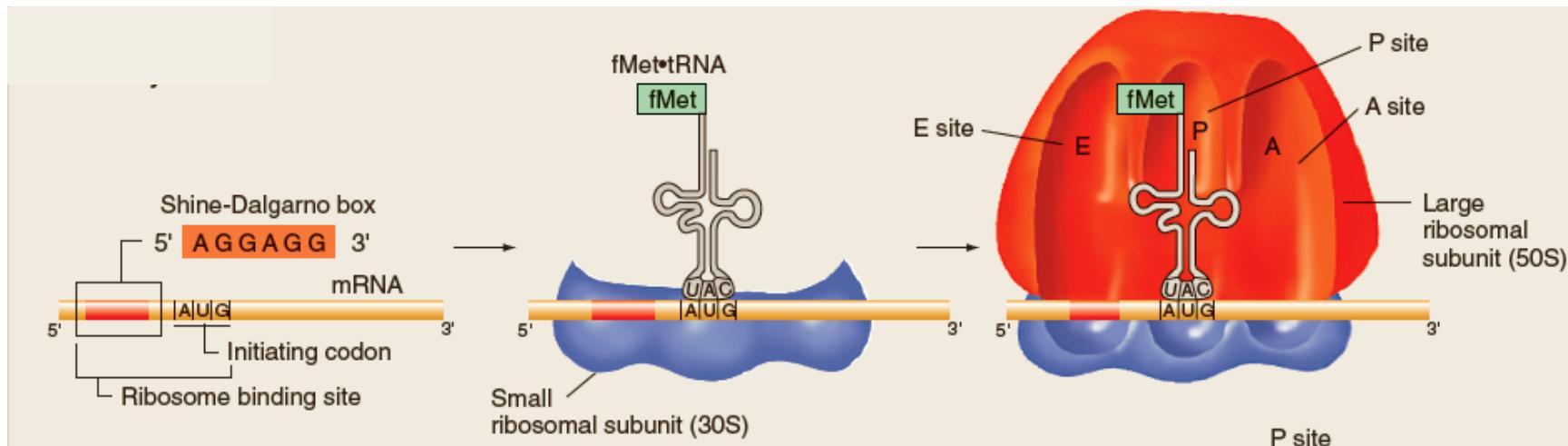


Fig. 8.25

Translation of mRNAs on ribosomes: Initiation phase in eukaryotes

Small ribosomal subunit binds to 5' cap, then scans the mRNA for the first AUG codon

Initiator tRNA carries Met (not fMet)

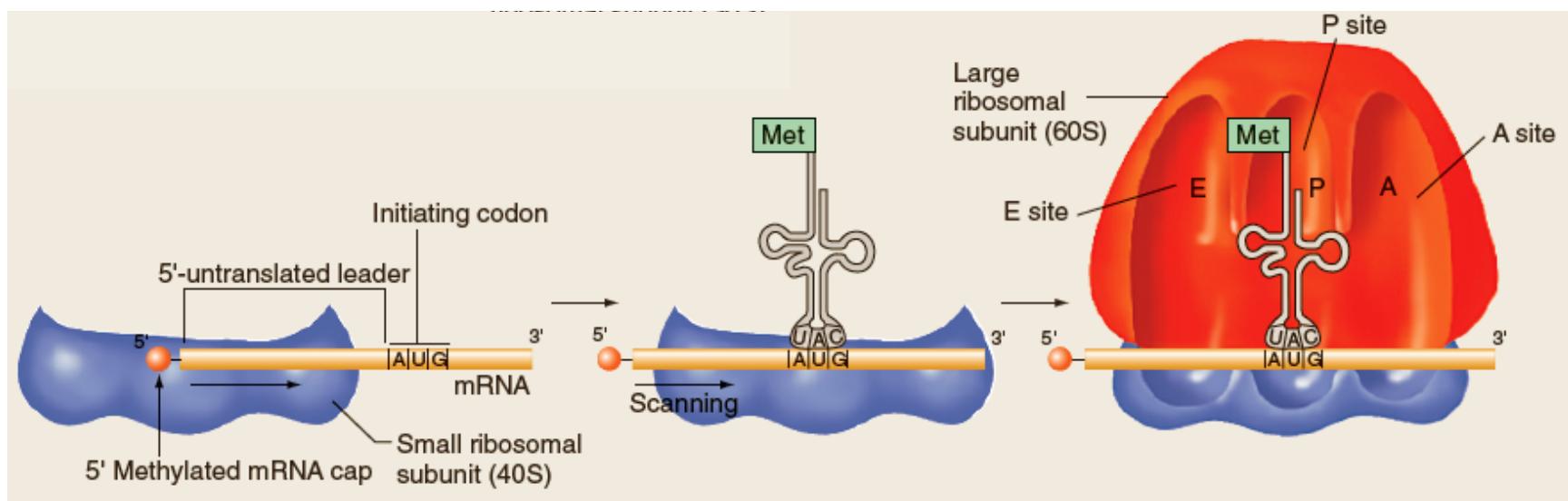
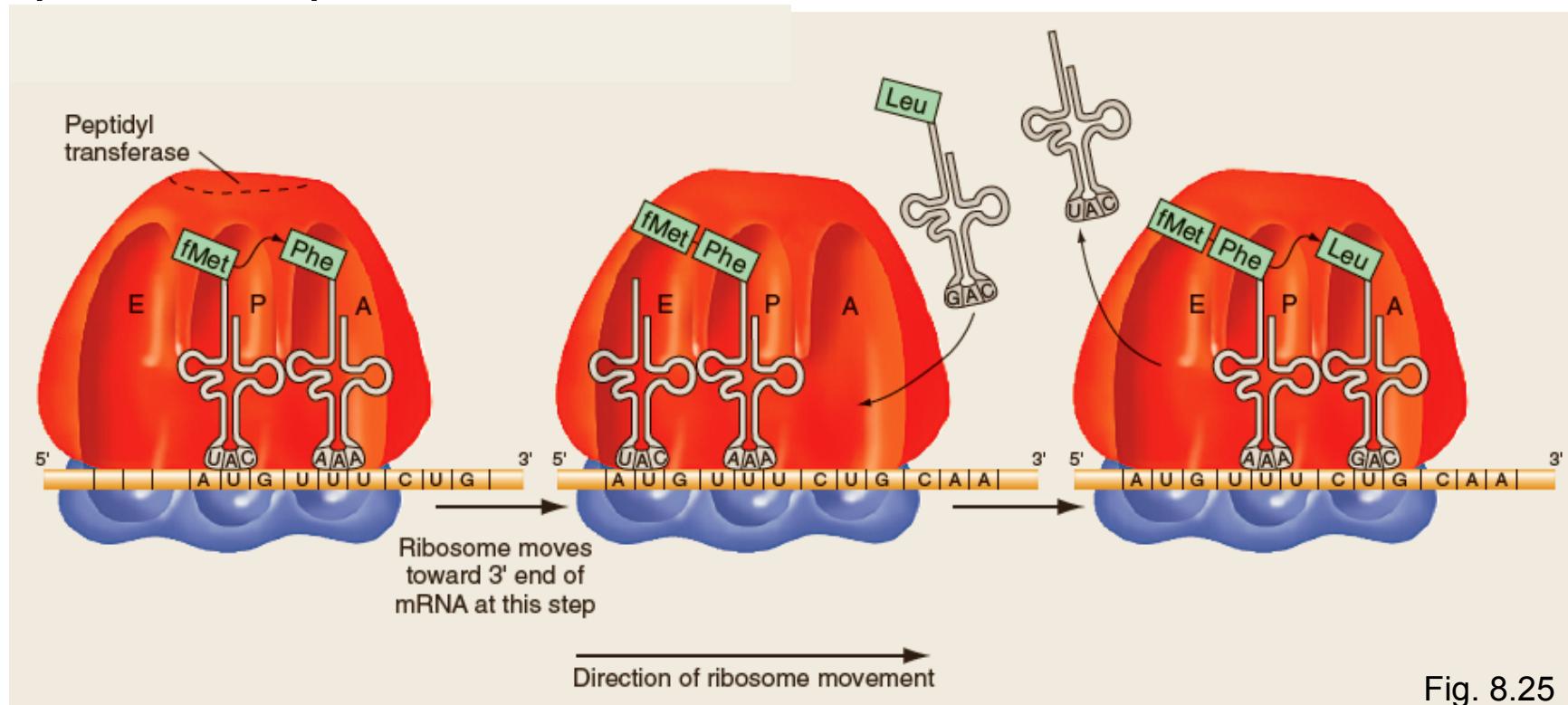


Fig. 8.25

Translation of mRNAs on ribosomes: Elongation phase

Addition of amino acids to C-terminus of polypeptide

Charged tRNAs ushered into A site by elongation factors
(not shown)



Polyribosomes consist of several ribosomes translating the same mRNA

Simultaneous synthesis of many copies of a polypeptide from a single mRNA

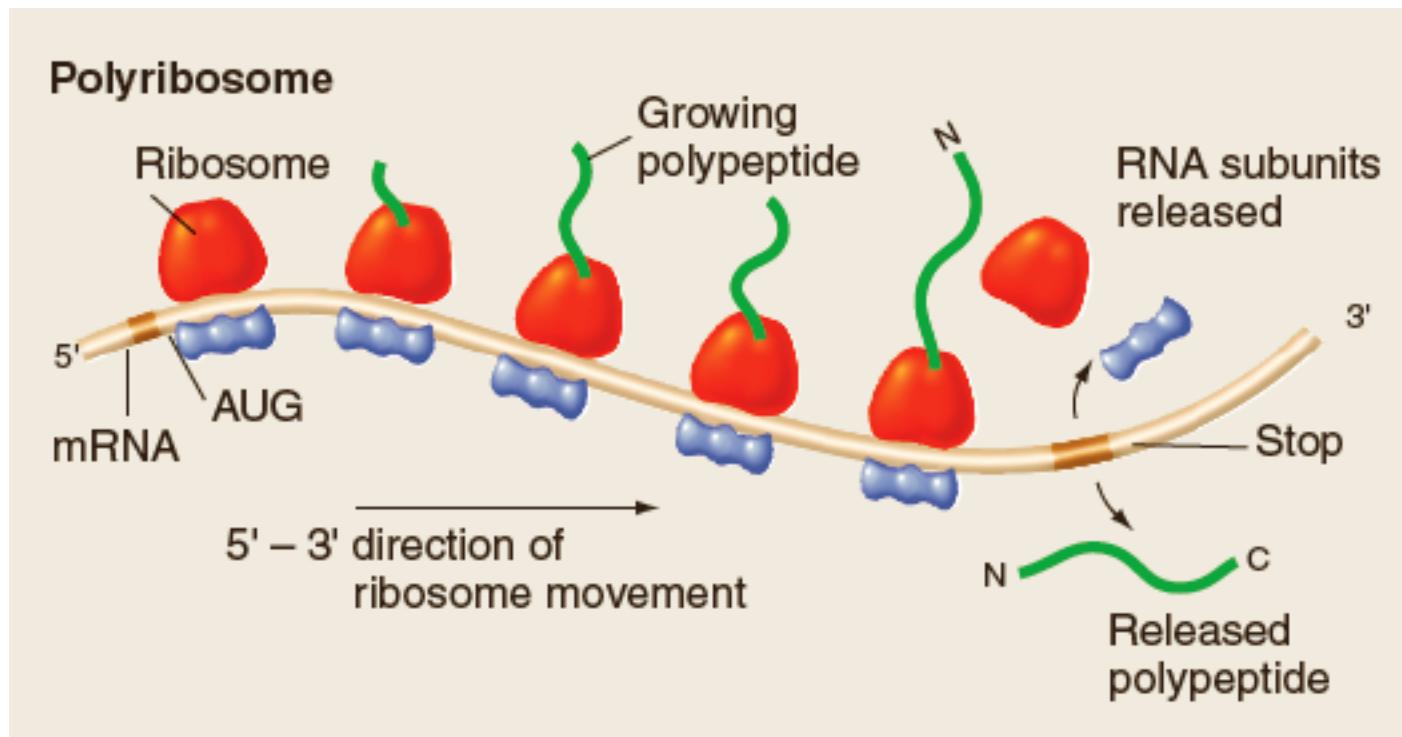


Fig. 8.25

Translation of mRNAs on ribosomes: Termination phase

No normal tRNAs carry anticodons for the stop codons

Release factors bind to the stop codons

Release of ribosomal subunits, mRNA, and polypeptide

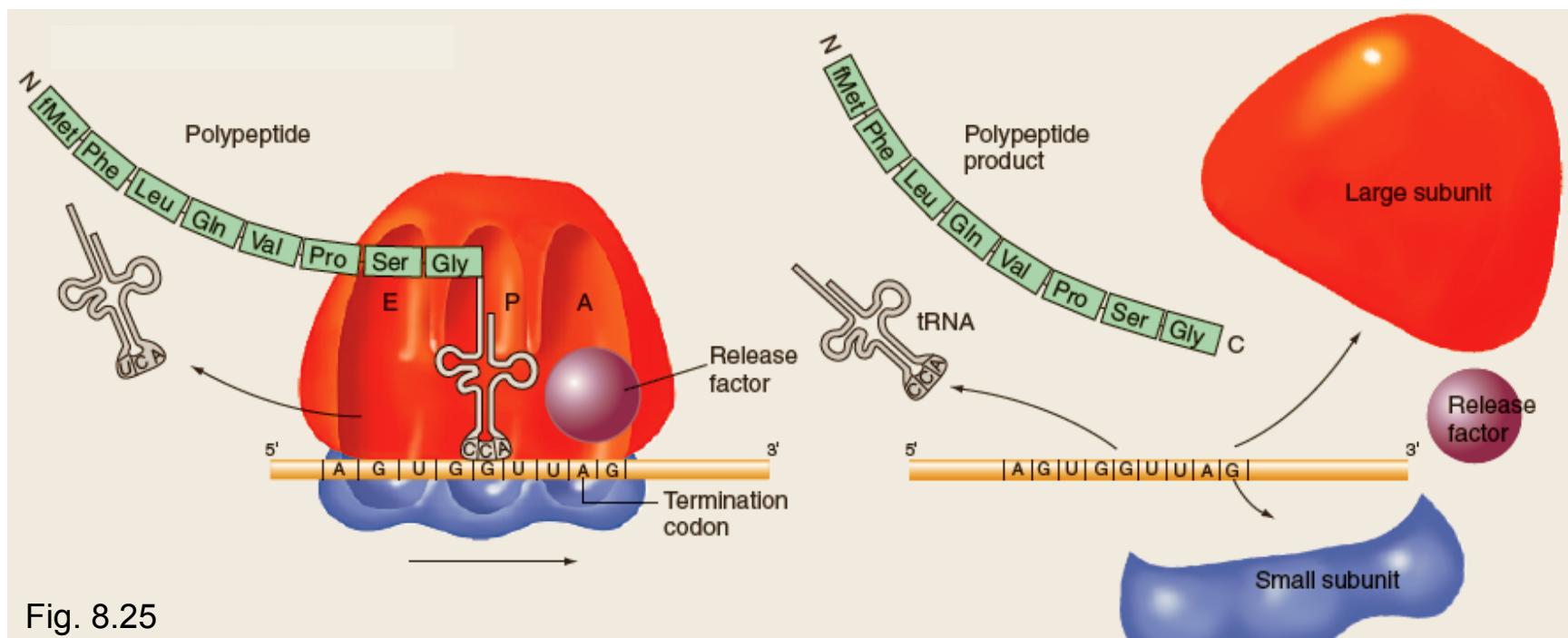
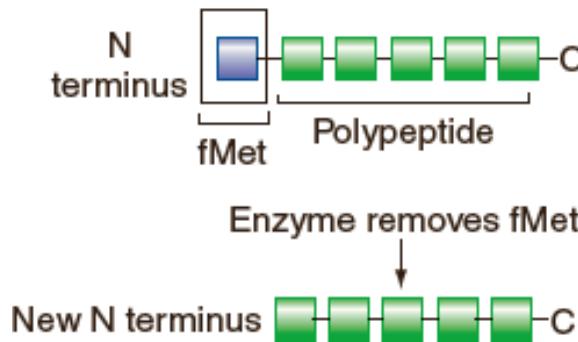


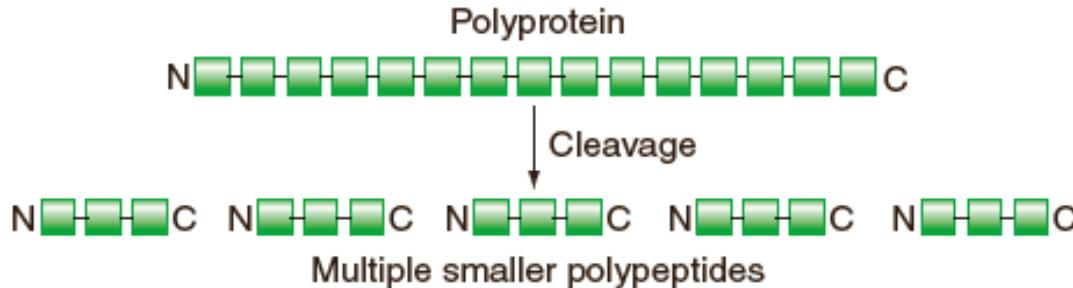
Fig. 8.25

Posttranslational processing can modify polypeptide structure

(a) Cleavage may remove an amino acid



(b) Cleavage may split a polyprotein



c) Chemical constituent addition

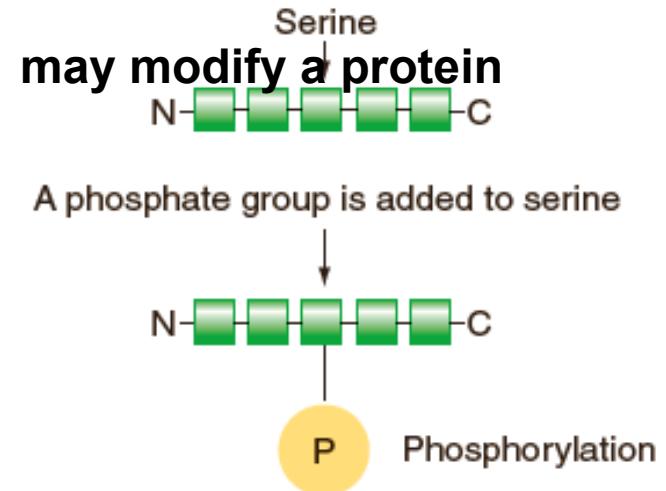


Fig. 8.26

CHAPTER OUTLINE

- **Gene Expression: The Flow of Information from DNA to RNA to Protein**
- 8.1 The Genetic Code
- 8.2 Transcription: From DNA to RNA
- 8.3 Translation: From mRNA to Protein
- 8.4 Differences in Gene Expression Between Prokaryotes and Eukaryotes
- 8.5 The Effect of Mutations on Gene Expression and Gene Function

Differences between prokaryotes and eukaryotes in gene expression

Overview

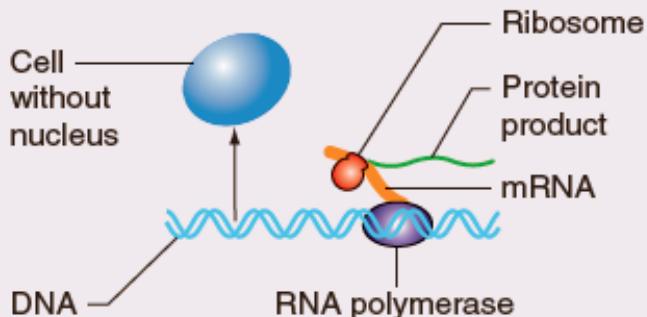
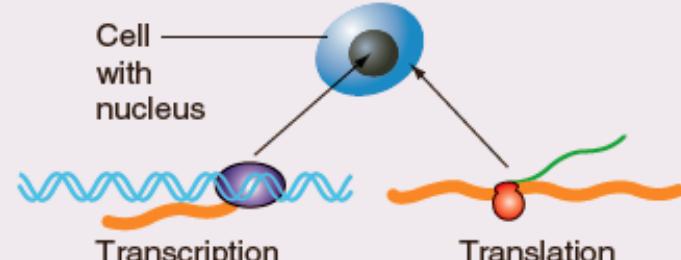
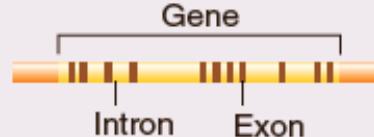
Prokaryotes	Eukaryotes
<p>1. No nucleus. Transcription and translation take place in the same cellular compartments, and translation is often coupled to transcription.</p>  <p>The diagram shows a blue spherical cell labeled 'Cell without nucleus'. Inside, a wavy blue line represents DNA. A purple oval labeled 'RNA polymerase' is shown transcribing the DNA into a green wavy line labeled 'mRNA'. An orange oval labeled 'Ribosome' is attached to the mRNA, translating it into a green line labeled 'Protein product'.</p>	<p>1. Nucleus separated from the cytoplasm by a nuclear membrane. Transcription takes place in the nucleus, while translation occurs in the cytoplasm. Direct coupling of transcription and translation is not possible.</p>  <p>The diagram shows a blue spherical cell labeled 'Cell with nucleus'. The interior is divided by a black circular boundary representing the nuclear membrane. On the left, a purple oval labeled 'RNA polymerase' is transcribing blue DNA into green mRNA within the nucleus. On the right, an orange oval labeled 'Ribosome' is translating the green mRNA into a protein product in the cytoplasm.</p>
<p>2. Genes are not divided into exons and introns.</p>  <p>A horizontal yellow bar represents a gene. A bracket above it is labeled 'Gene', indicating it is a single continuous segment.</p>	<p>2. The DNA of a gene consists of exons separated by introns; the exons are defined by posttranscriptional splicing, which deletes the introns.</p>  <p>A horizontal gene structure is shown with a bracket above it labeled 'Gene'. It consists of an orange segment labeled 'Intron' and two yellow segments labeled 'Exon'.</p>

Table 8.1

Differences between prokaryotes and eukaryotes in gene expression (cont)

Transcription

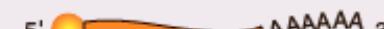
Prokaryotes	Eukaryotes
<ol style="list-style-type: none">1. One RNA polymerase consisting of five subunits.2. Primary transcripts are the actual mRNAs; they have a triphosphate start at the 5' end and no tail at the 3' end. 	<ol style="list-style-type: none">1. Several kinds of RNA polymerase, each containing 10 or more subunits; different polymerases transcribe different genes.2. Primary transcripts undergo processing to produce mature mRNAs that have a methylated cap at the 5' end and a poly-A tail at the 3' end. 

Table 8.1 (cont)

Differences between prokaryotes and eukaryotes in gene expression (cont)

Translation

Prokaryotes	Eukaryotes
1. Unique initiator tRNA carries formylmethionine.	1. Initiator tRNA carries methionine.
2. mRNAs have multiple ribosome binding sites and can thus direct the synthesis of several different polypeptides.	2. mRNAs have only one start site and can thus direct the synthesis of only one kind of polypeptide.
	
3. Small ribosomal subunit immediately binds to the mRNA's ribosome binding site.	3. Small ribosomal subunit binds first to the methylated cap at the 5' end of the mature mRNA and then scans the mRNA to find the ribosome binding site.
	

Table 8.1 (cont)

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Types of mutations in the coding sequence of genes

Wild-type mRNA

Wild-type polypeptide

Silent mutation

Missense mutation

Nonsense mutation

Frameshift mutation

Fig. 8.28a

5' GCU GGA GCA CCA GGA CAA GAU GGA 3'
N Ala Gly Ala Pro Gly Gln Asp Gly C

GCU GGA GCC CCA GGA CAA GAU GGA
Ala Gly Ala Pro Gly Gln Asp Gly

GCU GGA GCA CCA AGA CAA GAU GGA
Ala Gly Ala Pro Arg Gln Asp Gly

GCU GGA GCA CCA GGA UAA GAU GGA
Ala Gly Ala Pro Gly Stop Asp Gly

GCU GGA GCC ACC AGG ACA AGA UGG A
Ala Gly Ala Thr Arg Thr Arg Trp

Mutations in the coding sequence of a gene can alter the gene product

Missense mutations replace one amino acid with another

- **Conservative** – chemical properties of mutant amino acid are similar to the original amino acid
 - e.g. aspartic acid [(-)charged] → glutamic acid [(-)charged]
- **Nonconservative** – chemical properties of mutant amino acid are different from original amino acid
 - e.g. aspartic acid [(-)charged] → alanine (uncharged)

Mutations in the coding sequence of a gene can alter the gene product (cont)

Nonsense mutations change codon that encodes an amino acid to a stop codon (UGA, UAG, or UAA)

Frameshift mutations result from insertion or deletion of nucleotides with the coding region

- No frameshift if multiples of three are inserted or deleted

Silent mutations do not alter the amino acid sequence

- Degenerate genetic code – most amino acids have >1 codon

Mutations outside the coding sequence can disrupt gene expression

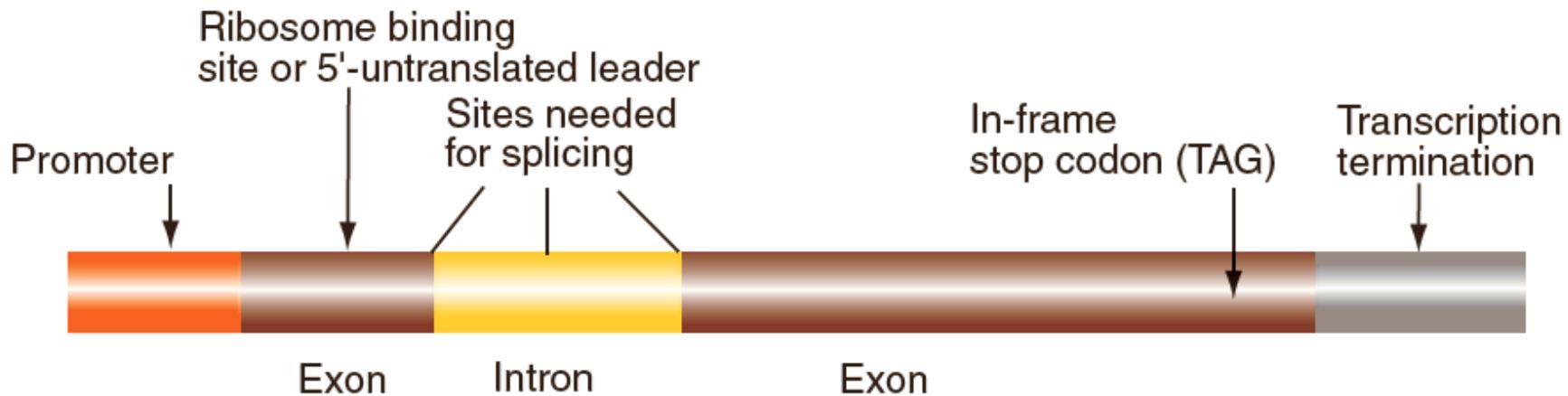


Fig. 8.28b

Loss-of-function mutations result in reduced or abolished protein activity

Loss-of-function mutations are usually recessive

- **Null (amorphic) mutations** – completely block function of a gene product (e.g. deletion of an entire gene)
- **Hypomorphic mutations** – gene product has weak, but detectable, activity

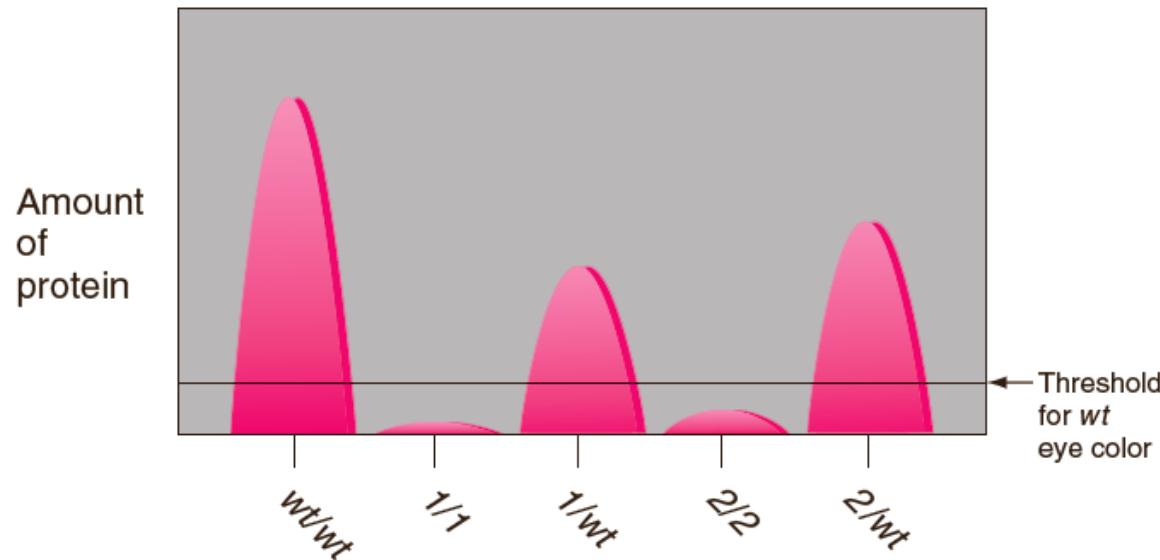


Fig. 8.29

Loss-of-function mutations result in reduced or abolished protein activity (cont)

Some loss-of-function mutations can be dominant

- **Incomplete dominance** – phenotype varies with the amount of functional gene product (Fig 8.30)
- **Haploinsufficiency** – phenotype is sensitive to gene dosage (i.e. 50% of gene product) (Fig 8.31a)

Fig. 8.30

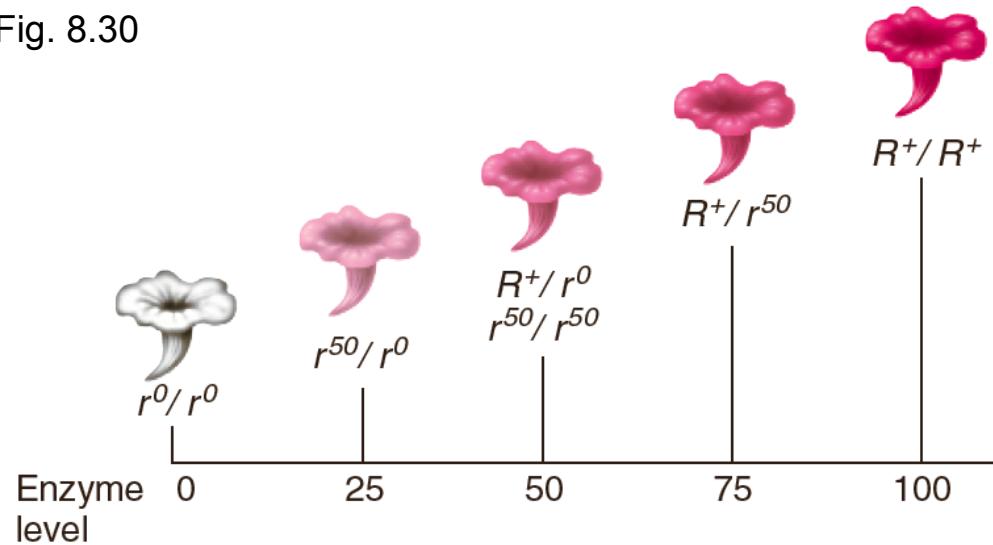
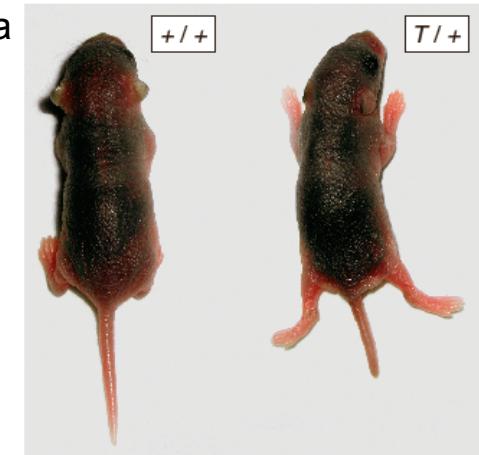


Fig. 8.31a



Loss-of-function mutations result in reduced or abolished protein activity (cont)

Some loss-of-function mutations can be **dominant-negative**

- Usually occurs in genes that encode multimeric proteins

Multimeric protein made of four subunits

Functional Enzyme	Nonfunctional Enzyme			
 $d^+d^+d^+d^+$	 $d^+d^+d^+D$	 $d^+d^+D d^+$	 $d^+ D d^+d^+$	 $Dd^+d^+d^+$
	 $d^+d^+D D$	 $d^+D D d^+$	 $d^+ D d^+D$	 $Dd^+D d^+$
	 $D d^+d^+D$	 $D D d^+d^+$	 $d^+ D D D$	 $Dd^+D D$
	 $D D d^+D$	 $D D D d^+$	 $D D D D$	

Kinky allele of *fused* locus



Fig. 8.31c

Mutant subunits block the activity of normal subunits

Fig. 8.31b

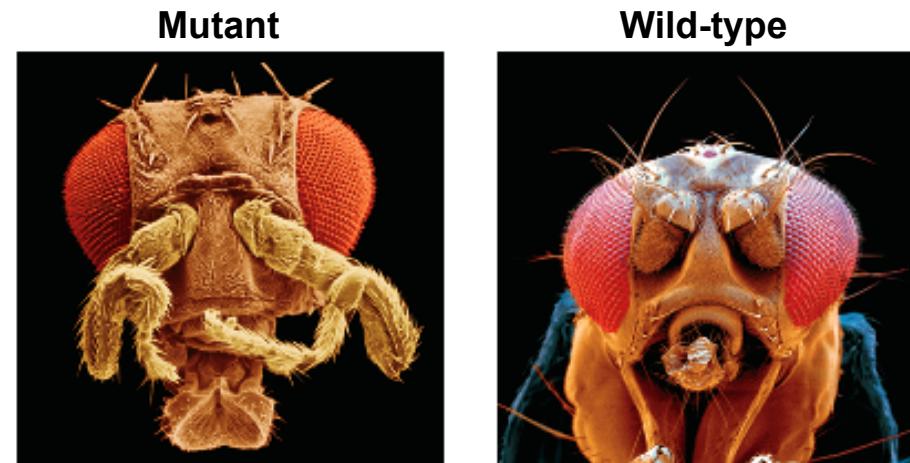
Gain-of-function mutations enhance a function or confer a new activity

Gain-of-function mutations are usually dominant

- **Hypermorphic mutations** – generate more gene product or the same amount of a more efficient gene product
- **Neomorphic mutations** – generate gene product with new function or that is expressed at inappropriate time or place

Mutation in *Antennapedia* gene of *Drosophila* causes **ectopic expression** of a leg-determining gene in structures that normally produce antennae

Fig. 8.31



Mutations classified by their effects on protein function

Loss-of-Function			
<i>Mutation Type</i>	Hypomorphic (leaky)	Amorphic (null)	Antimorphic (dominant negative)*
<i>Occurrence</i>	Common	Common	Rare
<i>Possible Dominance Relations</i>	Usually recessive to wild type Can be incompletely dominant if phenotype varies continuously with gene product Can be dominant in cases of haploinsufficiency		
Gain-of-Function			
<i>Mutation Type</i>	Hypermorphic	Neomorphic (ectopic expression)	
<i>Occurrence</i>	Rare	Rare	
<i>Possible Dominance Relations</i>	Usually dominant or incompletely dominant	Usually dominant or incompletely dominant	

Table 8.2

The cellular components of gene expression

Mutations in genes encoding gene products for transcription, RNA processing, translation, and protein processing are often lethal

Some mutations in tRNA genes can suppress mutations in protein-coding genes

Function	Cellular Components
<i>Transcription*</i>	Core RNA polymerase Sigma subunit Rho factor
<i>Splicing and RNA Processing</i>	snRNAs Protein components of spliceosomes Additional splicing factors Capping enzyme Methyl transferases Poly-A polymerase
<i>Translation</i>	mRNAs tRNAs Aminoacyl-tRNA synthetases rRNAs Protein components of ribosomes Translation factors
<i>Protein Processing</i>	Deformylases Amino peptidases Proteases Methylases Hydroxylases Glycosylases Kinases Phosphatases

Table 8.3

A nonsense mutation in a protein-coding gene creates a truncated, nonfunctional protein

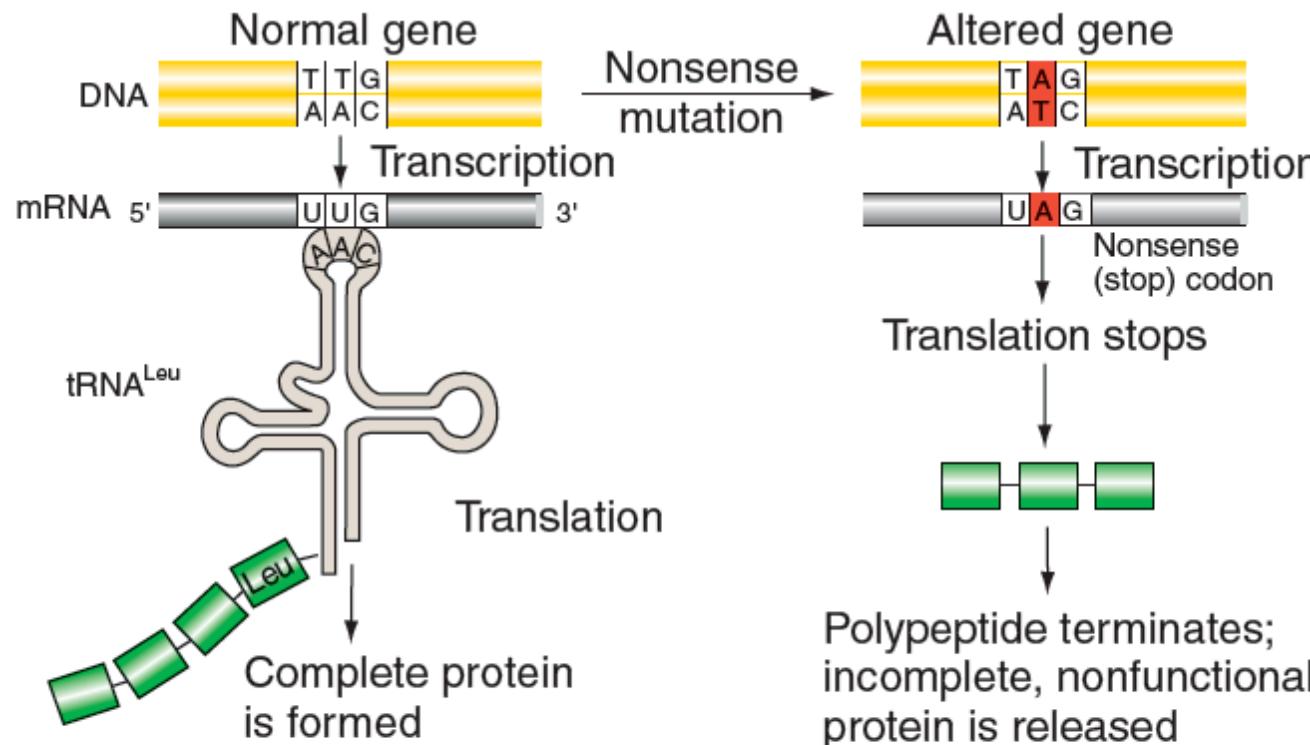
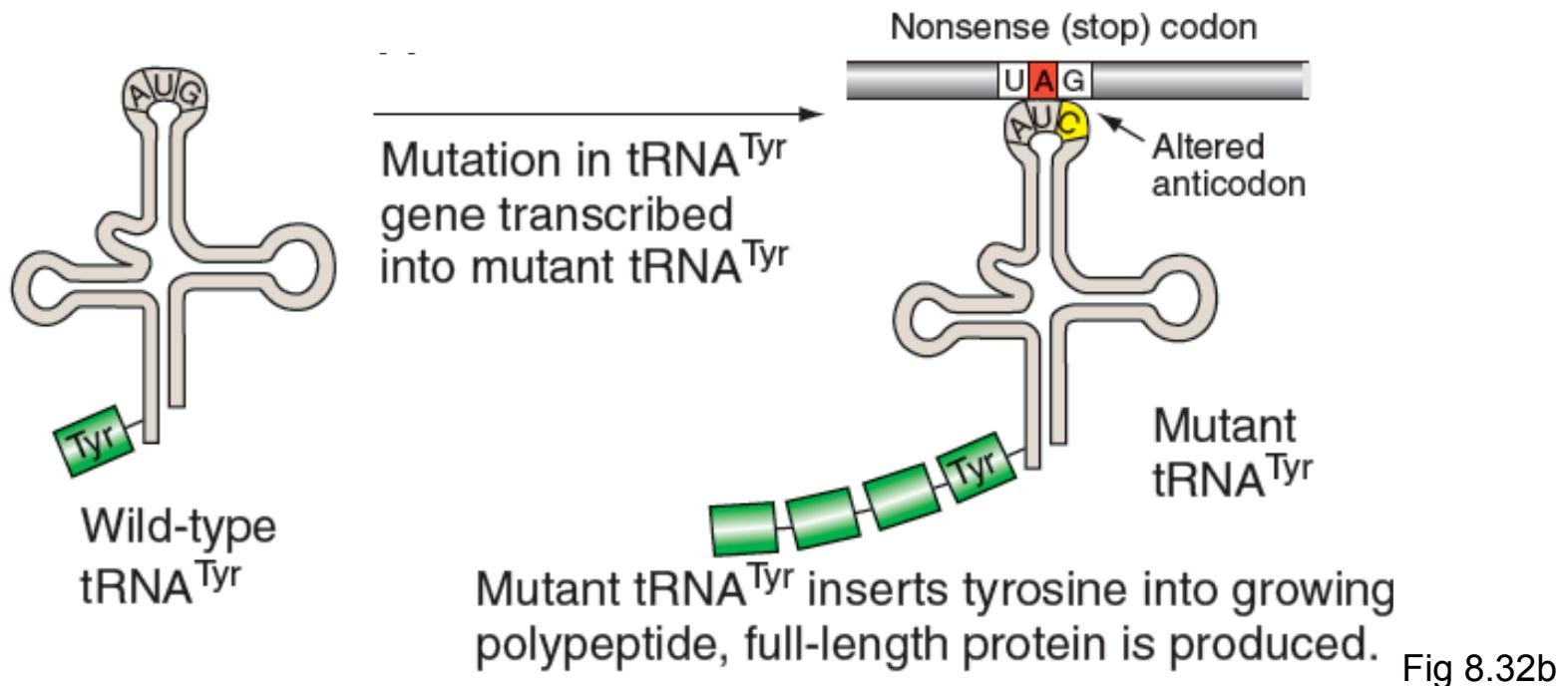


Fig 8.32a

Nonsense suppression

A second, nonsense suppressing mutation in the anticodon of a tRNA gene allows production of a (mutant) full-length polypeptide



[END]

Chapter 8 Questions