SEMESTER – III (THEORY)

C-7: MOLECULAR BIOLOGY

Unit 5 Translation (Prokaryotes and Eukaryotes)

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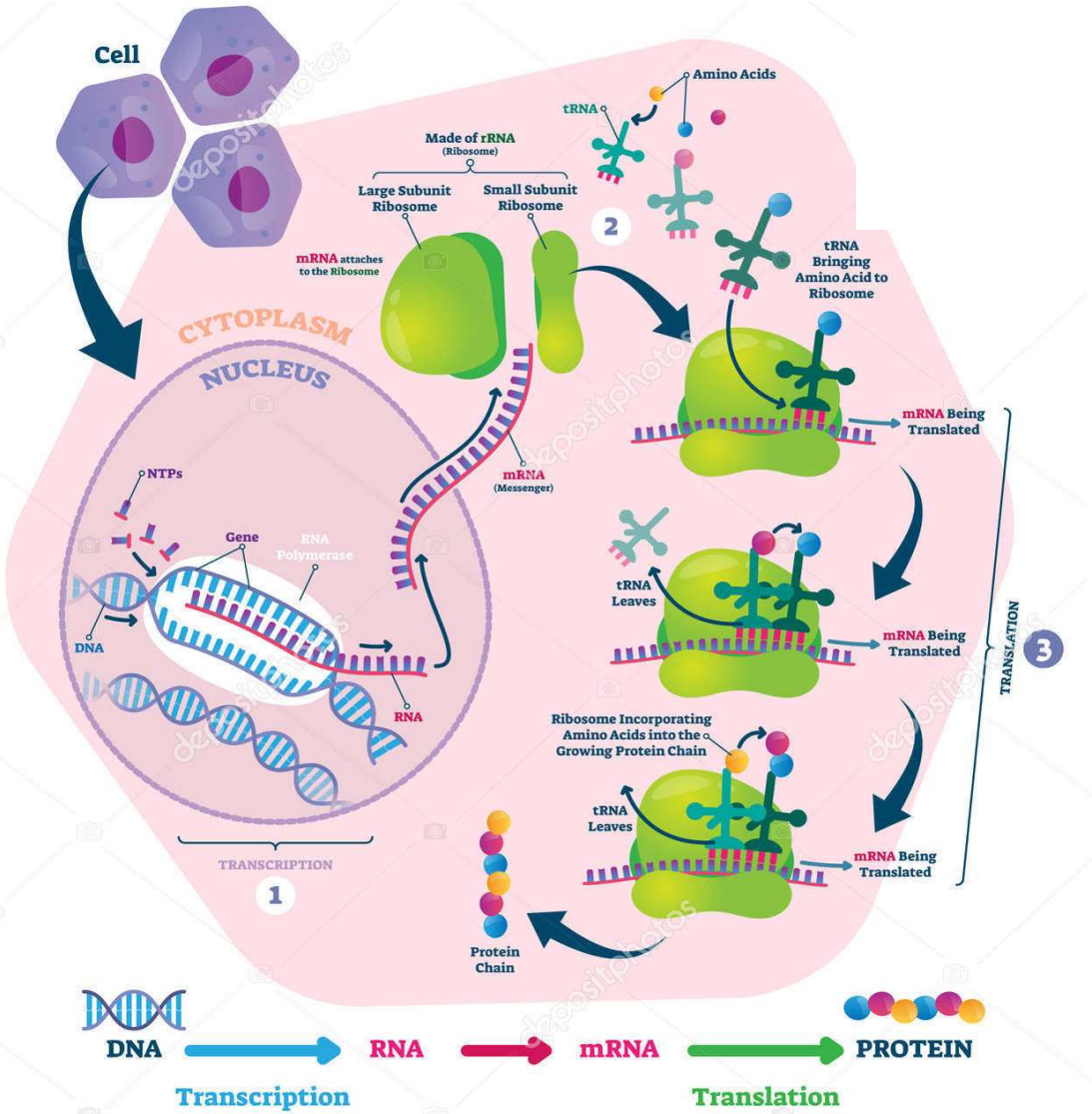
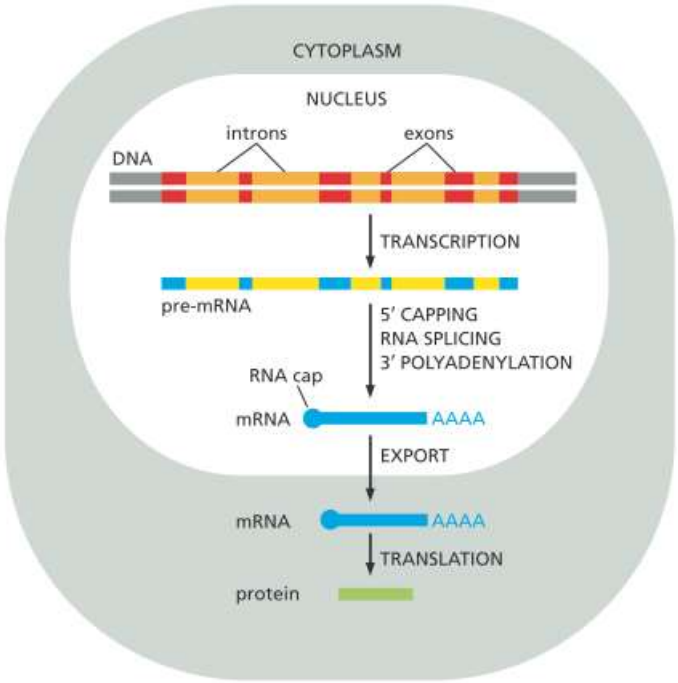
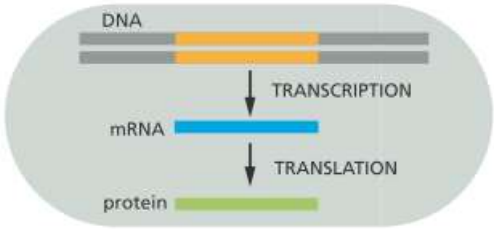
Translation: RNA to Protein





Eukaryotic cell



Prokaryotic cell

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The genetic basis for protein synthesis

- **Translation is a process in which the sequence of codons within mRNA provides the information to synthesize the sequence of amino acids that constitute a polypeptide. One or more polypeptides then fold and assemble to create a functional protein.**

- **The genes that encode the amino acid sequence of a polypeptide are known as protein-encoding genes or structural genes.**

- **Translation is among the most highly conserved across all organisms and among the most energetically costly for the cell.**

- **In rapidly growing bacterial cells, up to 80% of the cell's energy and 50% of the cell's dry weight are dedicated to protein synthesis.**

- **The machinery responsible for translating the language of mRNAs into the language of proteins is composed of four primary components: mRNAs, tRNAs, aminoacyl-tRNA synthetases and the ribosome.**

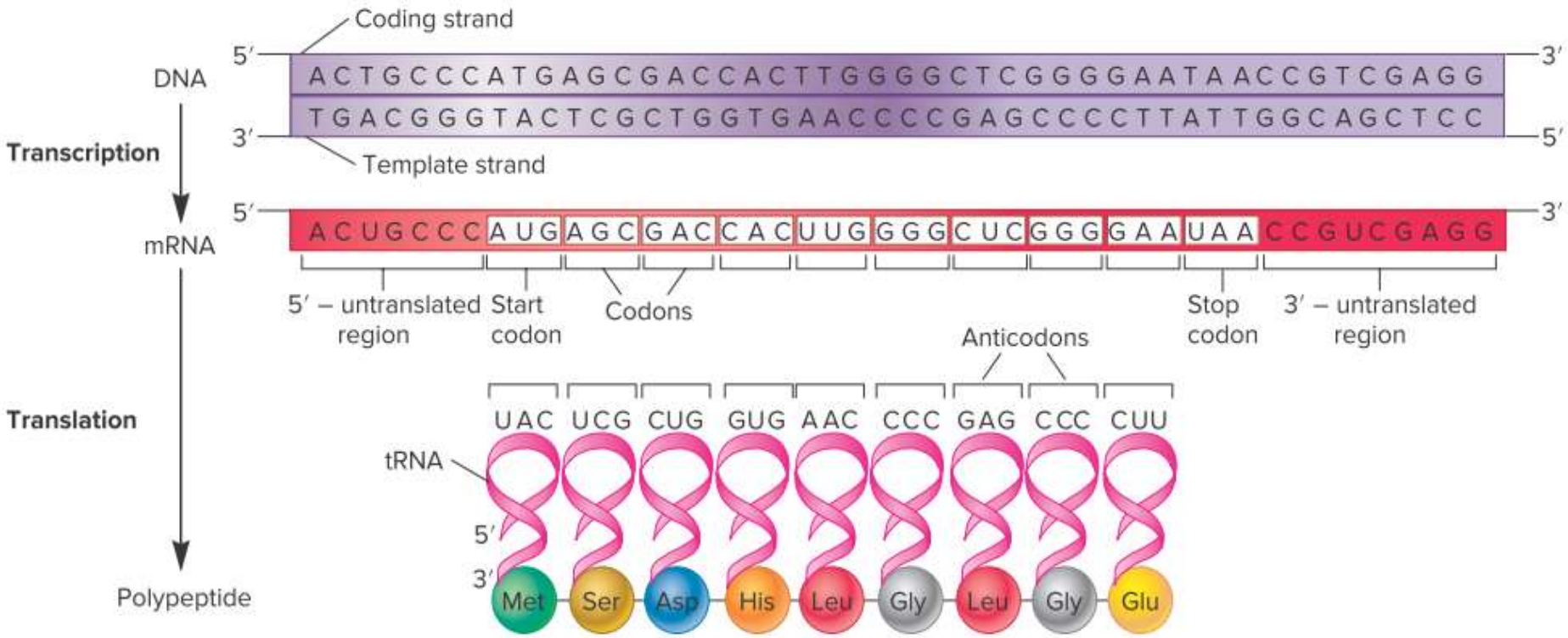
The relationship between the genetic code and protein synthesis

- **The ability of mRNA to be translated into a specific sequence of amino acids relies on the genetic code. The sequence of bases within an mRNA molecule provides coded information that is read in groups of three nucleotides known as codons.**

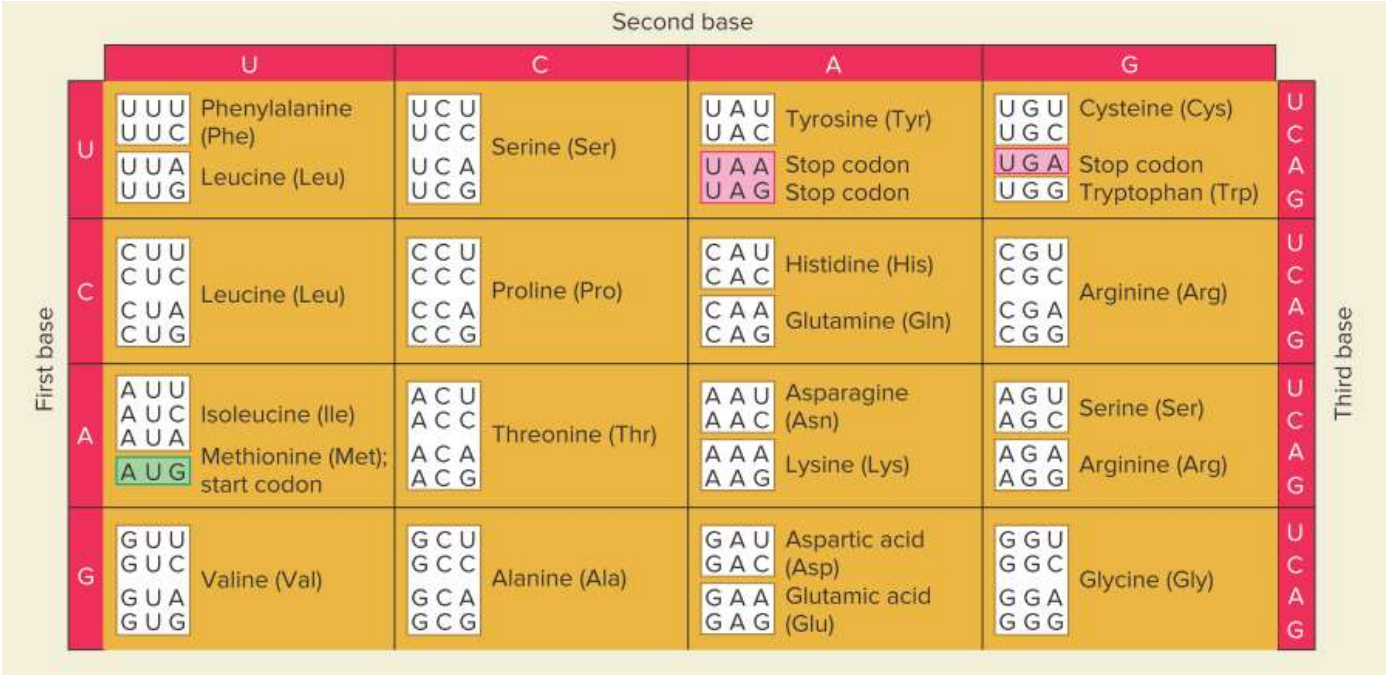
- **The sequence of three bases in most codons specifies a particular amino acid. These codons are termed sense codons. The codon AUG, which specifies methionine, is used as a start codon; three codons, UAA, UAG, and UGA, which are known as stop codons, are used to end the process of translation. Stop codons are also known as termination codons or nonsense codons.**

- **The codons in mRNA are recognized by the anticodons in transfer RNA (tRNA) molecules. Anticodons are three-nucleotide sequences that are complementary to codons in mRNA. The tRNA molecules carry the amino acids that are specified by the codons in the mRNA. In this way, the order of codons in mRNA dictates the order of amino acids within a polypeptide.**

The relationships among the DNA coding sequence, mRNA codons, tRNA anticodons, and amino acids in a polypeptide



- **In 1961, it was discovered that the sequence of nucleotides in an mRNA molecule is read consecutively in groups of three. RNA is made of 4 different nucleotides, so there are $4 \times 4 \times 4 = 64$ possible combinations of three nucleotides. Each group of three consecutive nucleotides in RNA is called a codon, and each codon specifies one amino acid.**
- **Har Gobind Khorana with Marshall W. Nirenberg and Robert W. Holley were awarded Nobel Prize in 1968 for Physiology or Medicine for research that helped to show how the nucleotides in nucleic acids, which carry the genetic code of the cell, control the cell's synthesis of proteins.**



Major features of the genetic code

GCA GCC GCG GCU	AGA AGG CGA CGC CGG CGU	GAC GAU	AAC AAU	UGC UGU	GAA GAG	CAA CAG	GGA GGC GGG GGU	CAC CAU	AUA AUC AUU	UUA UUG CUA CUC CUG CUU	AAA AAG	AUG	UUC UUU	CCA CCC CCG CCU	AGC AGU UCA UCC UCG UCU	ACA ACC ACG ACU	UGG	UAC UAU	GUA GUC GUG GUU	UAA UAG UGA
Ala	Arg	Asp	Asn	Cys	Glu	Gln	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val	stop
A	R	D	N	C	E	Q	G	H	I	L	K	M	F	P	S	T	W	Y	V	

Experiments by Marshall Nirenberg, Har Gobind Khorana, Francis Crick, Sydney Brenner, and others established the following features of the genetic code by 1961:

- ✓ **Three nucleotides encode an amino acid.**
- ✓ **The code is nonoverlapping.**
- ✓ **The code has no punctuation.**
- ✓ **The code has directionality.**
- ✓ **The genetic code is degenerate.**

This means that more than one codon can specify the same amino acid. The codons GGU, GGC, GGA, and GGG all specify the amino acid glycine. Such codons are termed synonymous codons. Only tryptophan and methionine are encoded by just one triplet each.

What is the biological significance of the extensive degeneracy of the genetic code?

If the code were not degenerate, 20 codons would designate amino acids and 44 would lead to chain termination. The probability of mutating to chain termination would therefore be much higher with a non-degenerate code. Chain-termination mutations usually lead to inactive proteins, whereas substitutions of one amino acid for another are usually rather harmless. Moreover, the code is constructed such that a change in any single nucleotide base of a codon results in a synonym or an amino acid with similar chemical properties. Thus, degeneracy minimizes the deleterious effects of mutations.

- **Inspection of the code shows that XYC and XYU always encode the same amino acid, and XYG and XYA usually encode the same amino acid as well.**

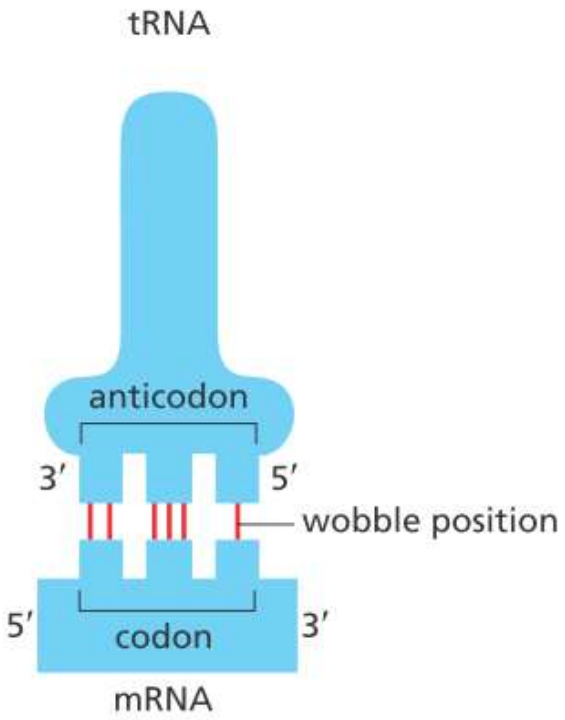
- **By combining structural insight with logical deduction, Crick proposed the wobble hypothesis to explain how a tRNA can recognize several degenerate codons. He assumed that *the first two codon–anticodon pairings have normal Watson–Crick geometry and that there could be a small amount of play or "wobble" in the third anticodon position to allow limited conformational adjustments in its pairing geometry*. This permits the formation of several non-Watson–Crick pairs such as U · G and I · A**

bacteria

wobble codon base	possible anticodon bases
U	A, G, or I
C	G or I
A	U or I
G	C or U

eukaryotes

wobble codon base	possible anticodon bases
U	A, G, or I
C	G or I
A	U
G	C



Wobble base-pairing between codons and anticodons

Structure and function of tRNA

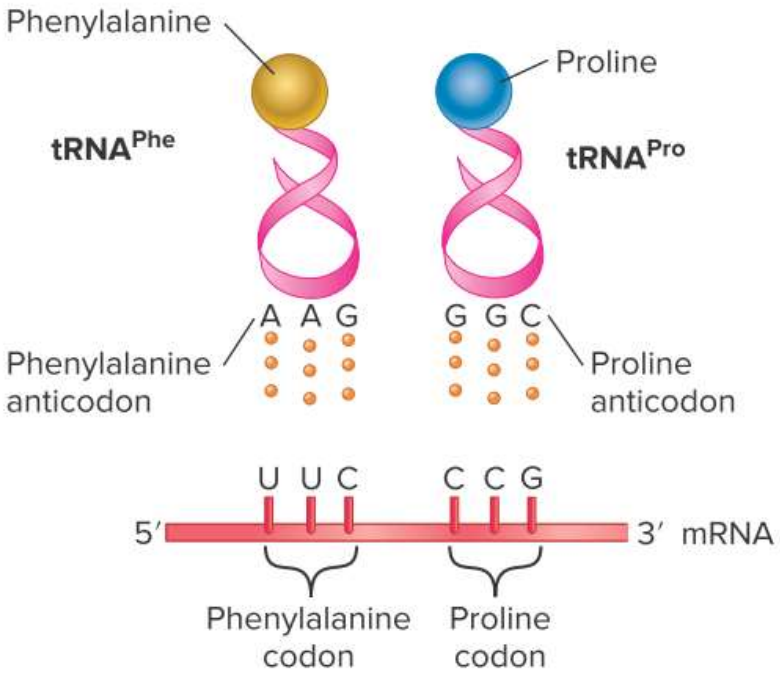
Francis Crick proposed the adaptor hypothesis. According to this idea, the position of an amino acid within a polypeptide is determined by the binding between the mRNA and an adaptor molecule carrying a specific amino acid. Later, work by Paul Zamecnik and Mahlon Hoagland suggested that the adaptor molecule is tRNA.

During translation, a tRNA has two functions:

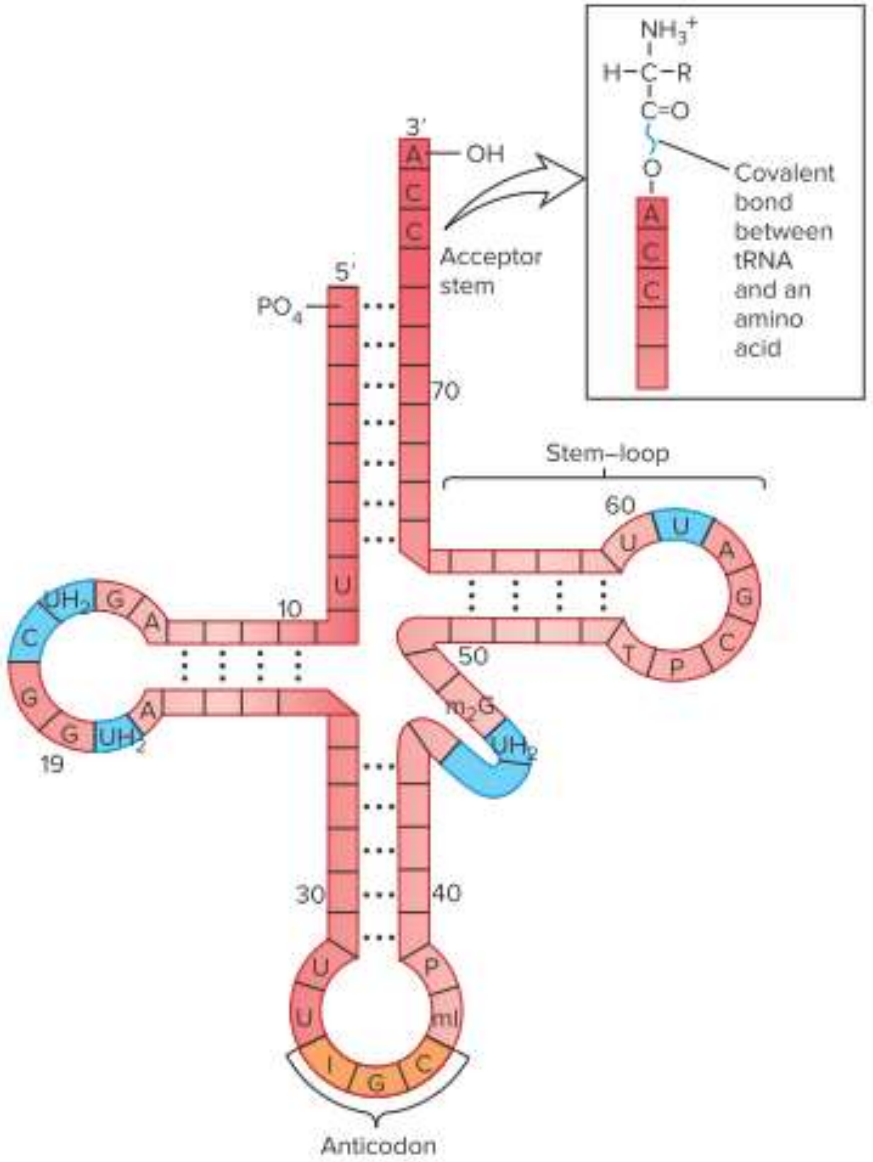
(1) It recognizes a three-base codon sequence in mRNA.

(2) it carries an amino acid specific for that codon.

The adaptor hypothesis proposes that *tRNA molecules recognize the codons within mRNA and carry the correct amino acids to the site of polypeptide synthesis*. During mRNA-tRNA recognition, the anticodon in a tRNA molecule binds to a codon in mRNA in an antiparallel manner and according to the AU/GC rule.



Recognition between tRNAs and mRNA



Secondary structure of tRNA

All tRNAs end at the 3' terminus with the sequence 5'-CCA-3'

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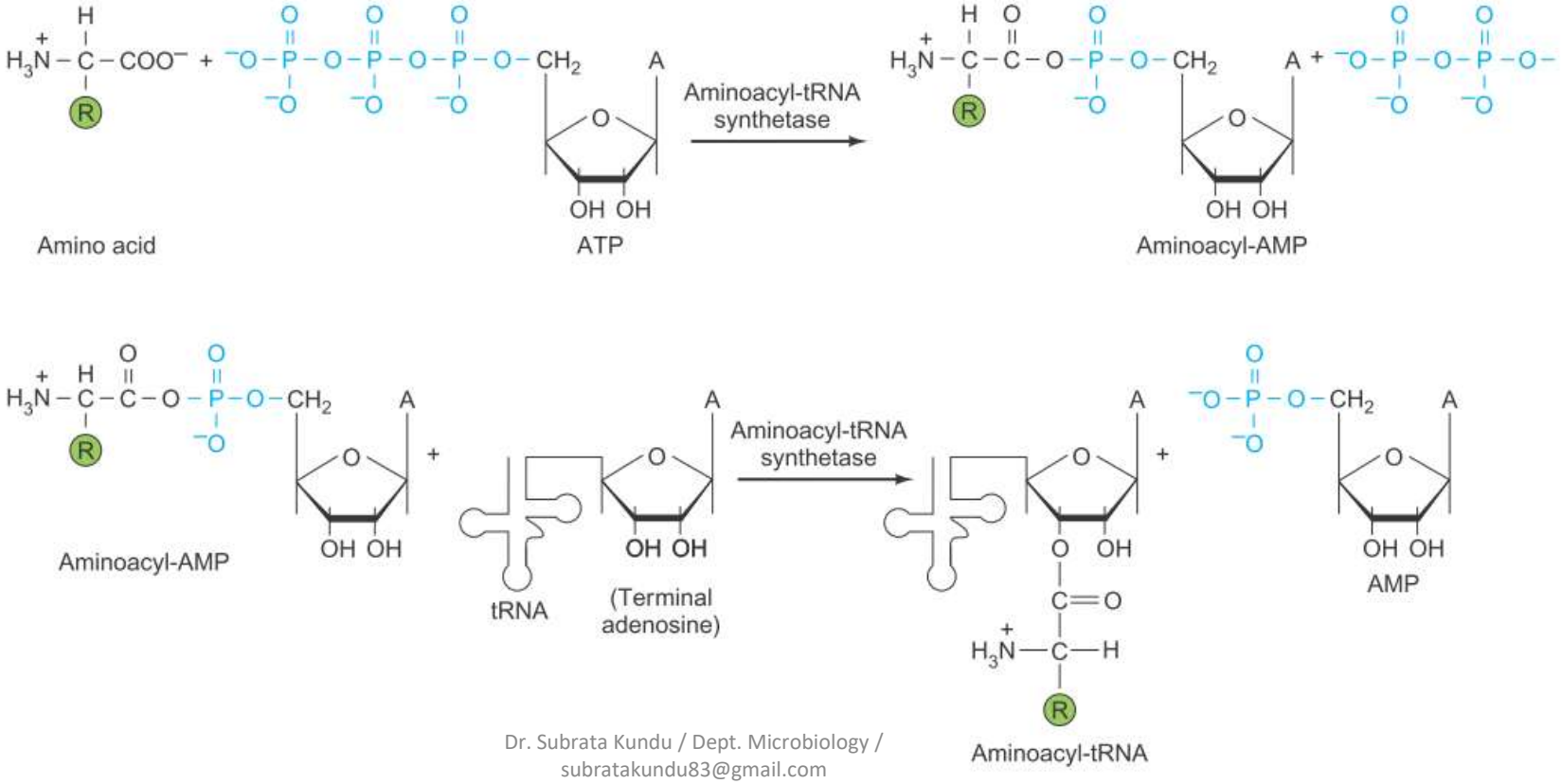
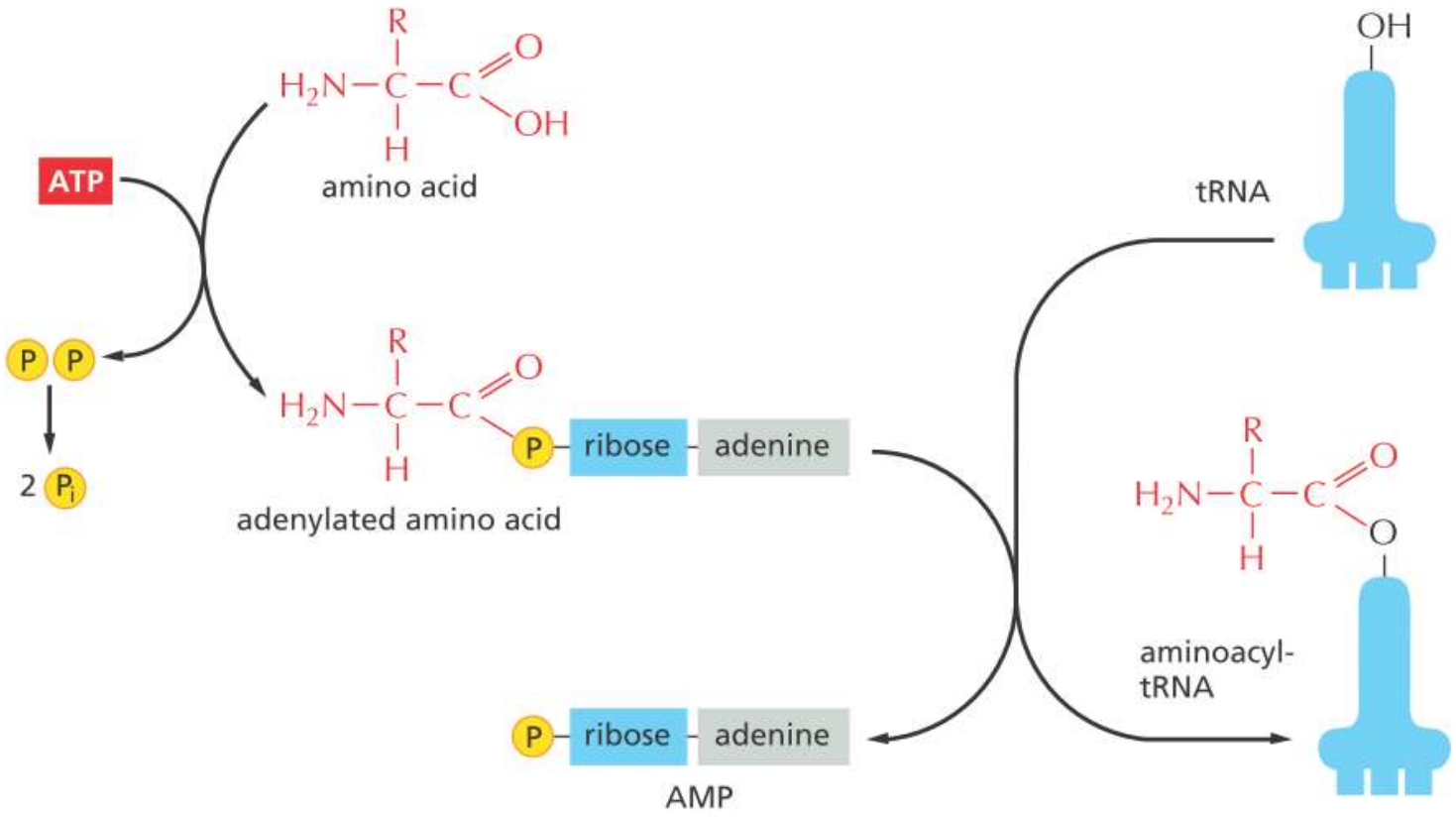
Aminoacyl-tRNA Synthetases Charge tRNAs by Attaching the Appropriate Amino Acid

- **Recognition and attachment of the correct amino acid depends on enzymes called aminoacyl-tRNA synthetases, which covalently couple each amino acid to its appropriate set of tRNA molecules.**
- **Most cells have a different synthetase enzyme for each amino acid (that is, 20 synthetases in all).**



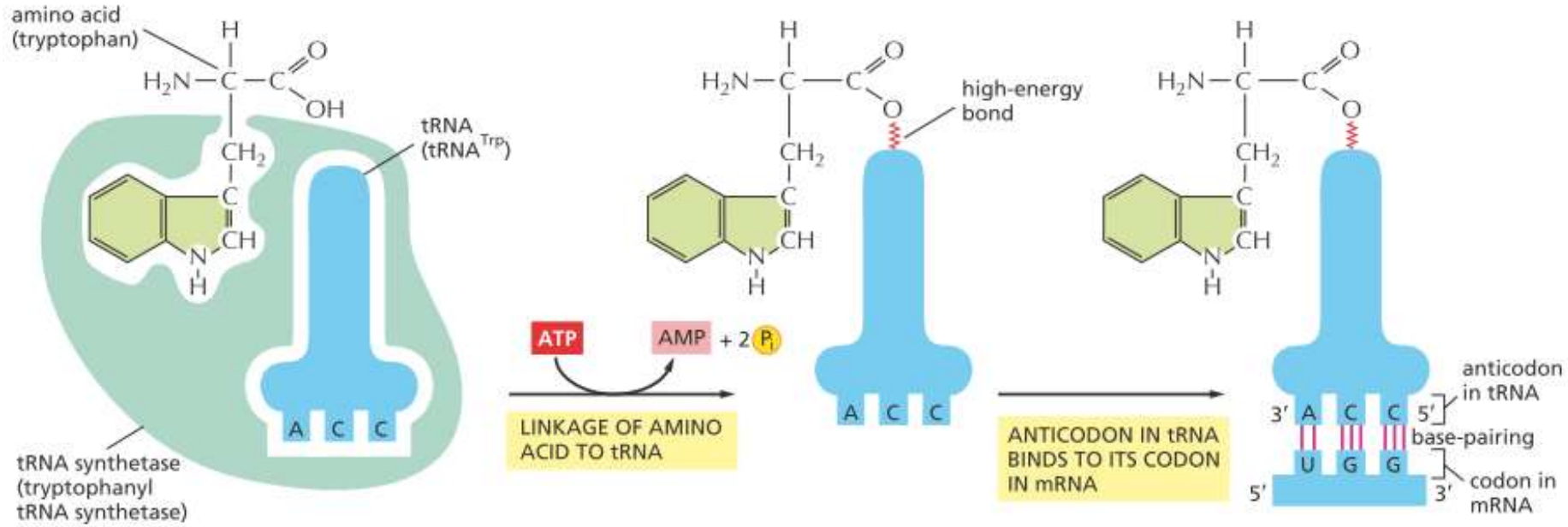


The synthetase-catalyzed reaction that attaches the amino acid to the 3′ end of the tRNA is coupled reaction to the energy-releasing hydrolysis of ATP, and it produces a high-energy bond between the tRNA and the amino acid. The energy of this bond is used at a later stage in protein synthesis to link the amino acid covalently to the growing polypeptide chain.

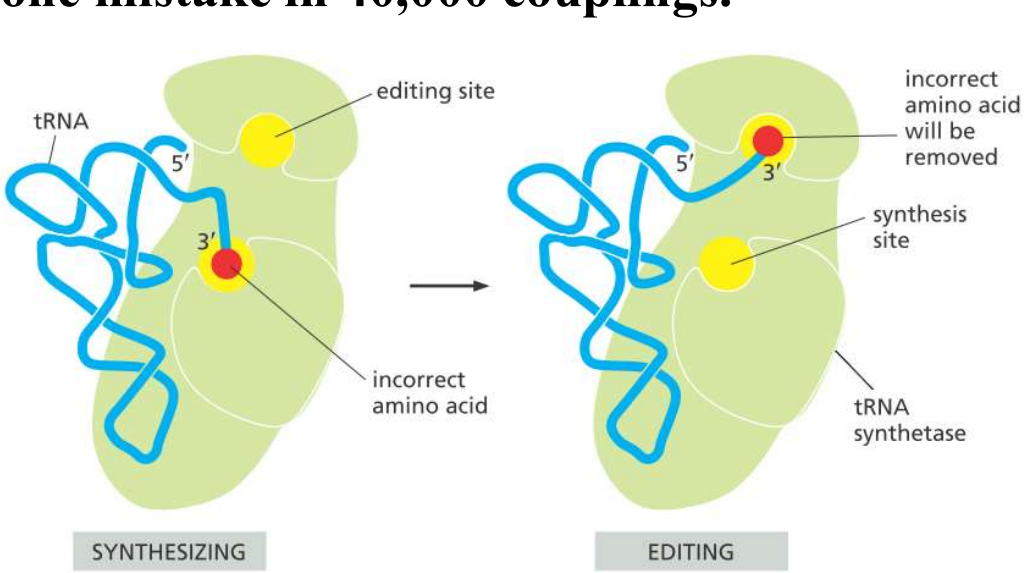
Editing by tRNA Synthetases Ensures Accuracy

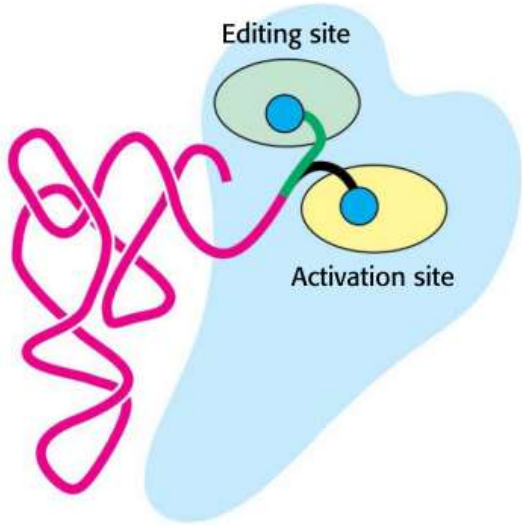
- **Most synthetase enzymes select the correct amino acid by a two-step mechanism. Proofreading by aminoacyl-tRNA synthetases increases the fidelity of protein synthesis**

- **The correct amino acid has the highest affinity for the active-site pocket of its synthetase and is therefore favored over the other.**



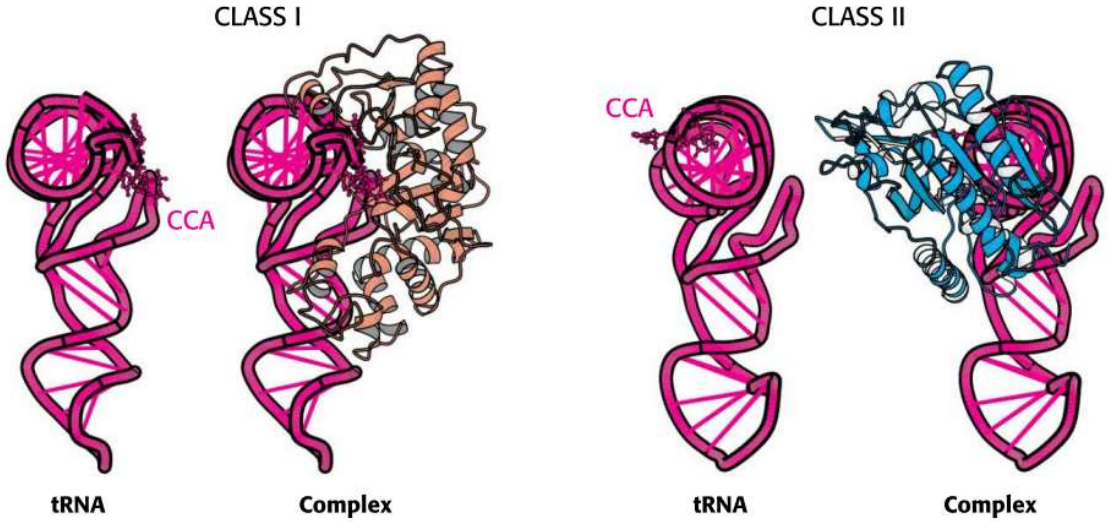
- **A second discrimination step occurs after the amino acid has been covalently linked to AMP. When tRNA binds, the synthetase tries to force the adenylated amino acid into a second editing pocket in the enzyme. The precise dimensions of this pocket exclude the correct amino acid, while allowing access by closely related amino acids. In the editing pocket, an amino acid is removed from the AMP (or from the tRNA itself if the aminoacyl-tRNA bond has already formed) by hydrolysis. This hydrolytic editing increases the overall accuracy of tRNA charging to approximately one mistake in 40,000 couplings.**





The flexible CCA arm of an aminoacyl-tRNA can move the amino acid between the activation site and the editing site. If the amino acid fits well into the editing site, the amino acid is removed by hydrolysis.

Aminoacyl-tRNA synthetases fall into two classes, termed class I and class II, each of which includes enzymes specific for 10 of the 20 amino acids. Intriguingly, synthetases from the two classes bind to different faces of the tRNA molecule. The CCA arm of tRNA adopts different conformations to accommodate these interactions; the arm is in the helical conformation observed for free tRNA for class II enzymes and in a hairpin conformation for class I enzymes.



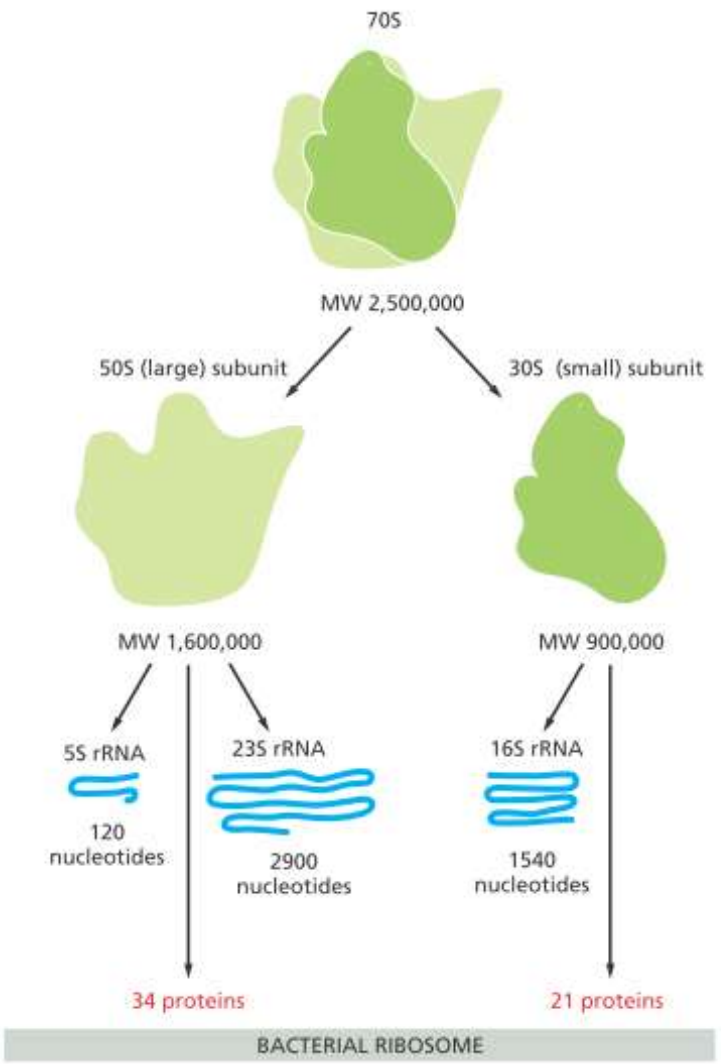
1. Class I enzymes acylate the 2′-hydroxyl group of the terminal adenosine of tRNA, whereas class II enzymes (except the enzyme for Phe-tRNA) acylate the 3′- hydroxyl group.
2. The two classes bind ATP in different conformations.
3. Most class I enzymes are monomeric, whereas most class II enzymes are dimeric.

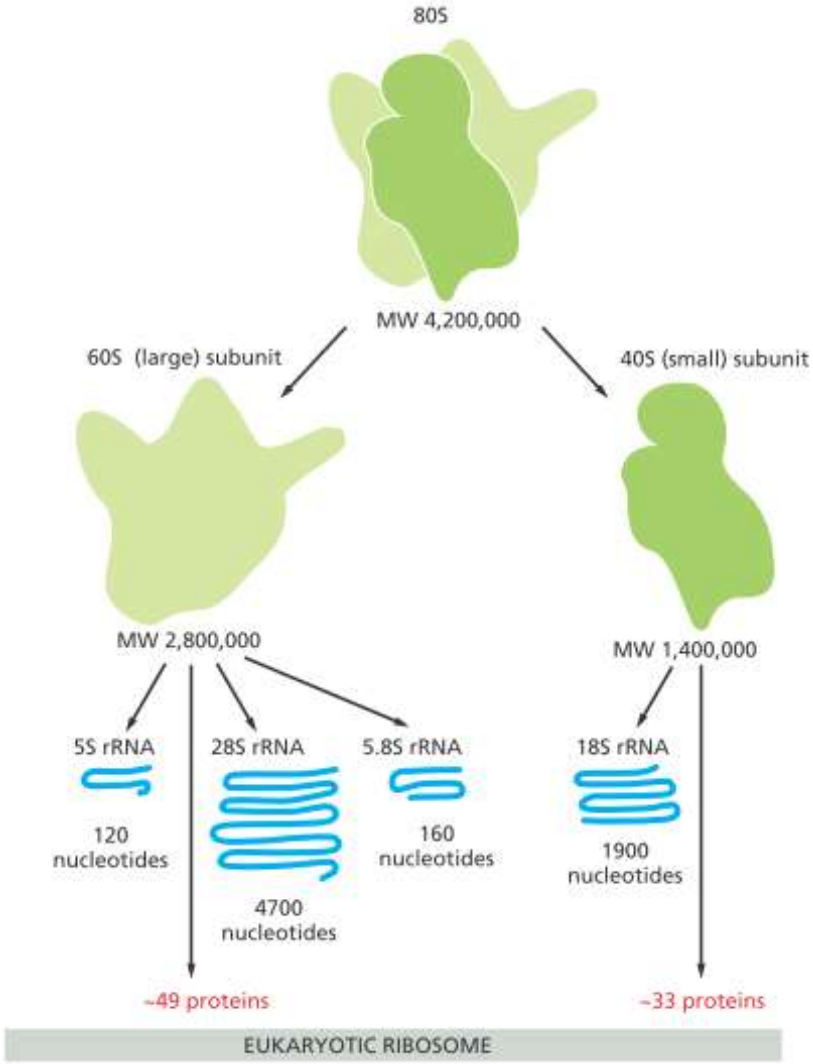
Ribosome structure and assembly

Bacterial and Eukaryotic ribosomes are assembled from rRNA and proteins. The synthesis of eukaryotic rRNA occurs within the nucleus, and the ribosomal proteins are made in the cytosol. The assembly of the rRNAs and ribosomal proteins to make the 40S and 60S subunits occurs within the nucleolus. The 40S and 60S subunits are then exported into the cytosol, where they associate to form an 80S ribosome during translation.

	 Small subunit	 Large subunit	 Assembled ribosome
Bacterial			
Sedimentation coefficient	30S	50S	70S
Number of proteins	21	34	55
rRNA molecule(s)	16S rRNA	5S rRNA, 23S rRNA	16S rRNA, 5S rRNA, 23S rRNA
Eukaryotic			
Sedimentation coefficient	40S	60S	80S
Number of proteins	33	49	82
rRNA molecule(s)	18S rRNA	5S rRNA, 5.8S rRNA, 28S rRNA	18S rRNA, 5S rRNA, 5.8S rRNA, 28S rRNA

A comparison of bacterial and eukaryotic ribosomes





mRNA

- **The protein-coding region(s) of each mRNA is composed of a contiguous, non-overlapping string of codons called an open reading frame (commonly known as an ORF). Each ORF specifies a single protein and starts and ends at internal sites within the mRNA.**

- **Translation starts at the 5′ end of the ORF and proceeds one codon at a time to the 3′ end. The first and last codons of an ORF are known as the start and stop codons. In bacteria, the start codon is usually 5′-AUG-3′, but 5′-GUG-3′ and sometimes even 5′ -UUG-3′ are also used.**

- **Eukaryotic cells always use 5′ -AUG-3′ as the start codon.**

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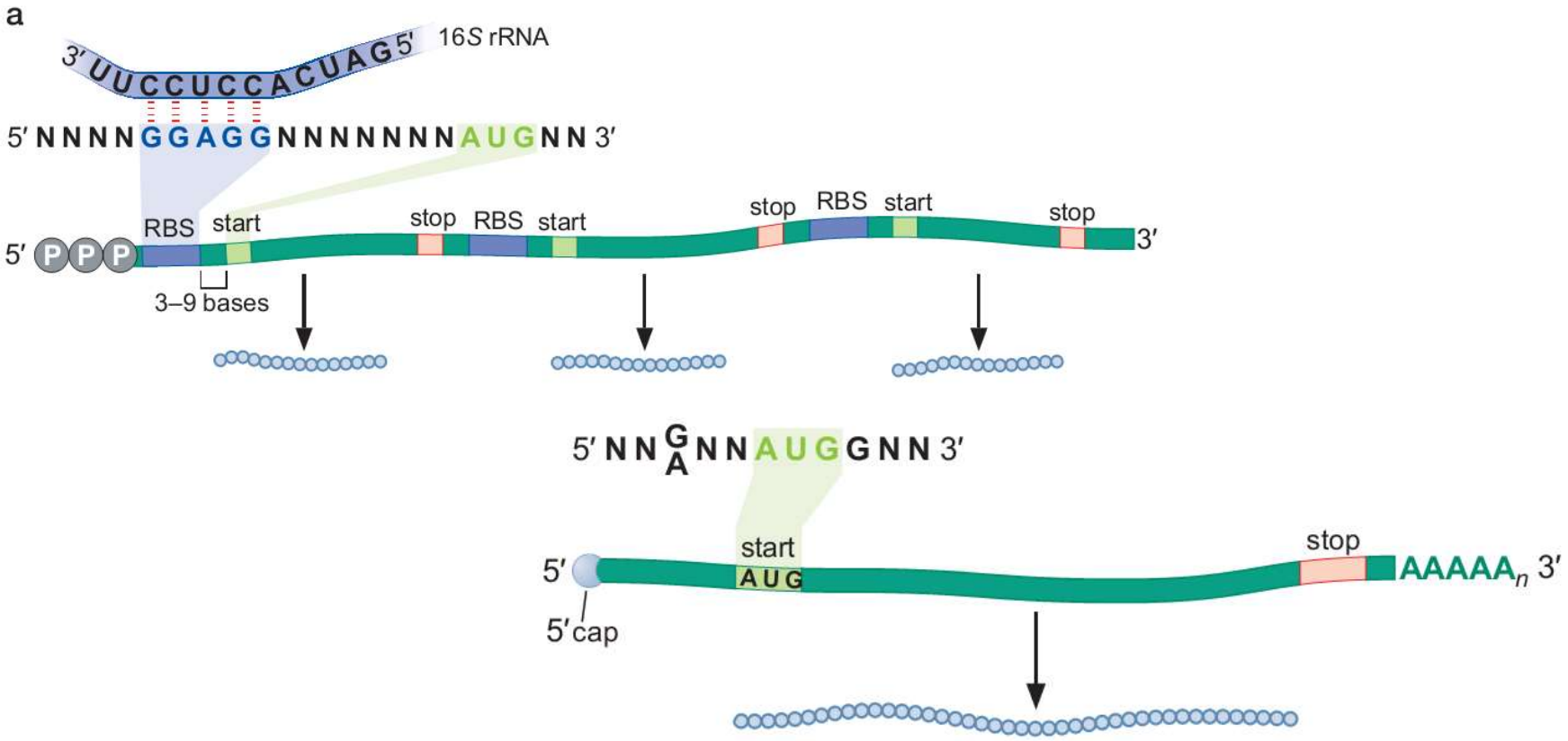
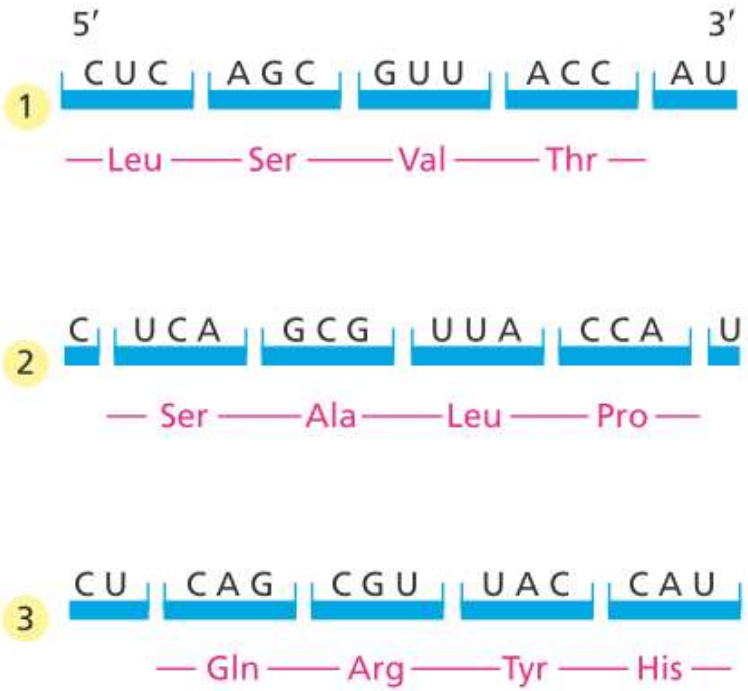
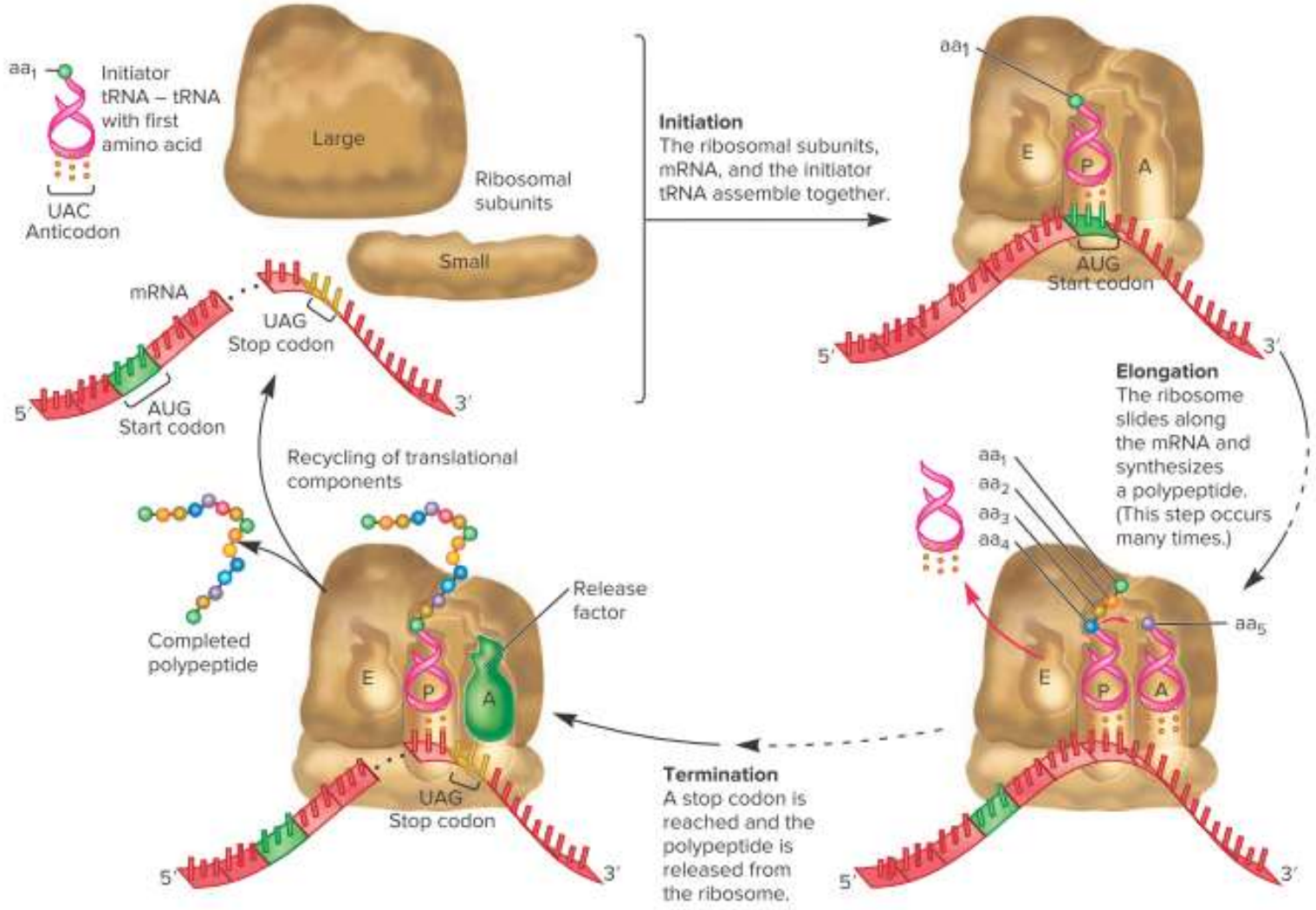
Eukaryotic mRNAs almost always contain a single ORF. In contrast, prokaryotic mRNAs frequently contain two or more ORFs and hence can encode multiple polypeptide chains. mRNAs containing multiple ORFs are known as polycistronic mRNAs, and those encoding a single ORF are known as monocistronic mRNAs.



Since the genetic code is read in groups of three bases, any nucleic acid sequence contains three possible reading frames. Any sequence of DNA or RNA, beginning with a start codon, and which can, at least theoretically, be translated into a protein, is known as an open reading frame. Between the 5′ end and the coding sequence is a short region that is not translated—the 5′ -untranslated region or 5′-UTR (sometimes 5′-nontranslated region or 5′-NTR).



Stages of translation

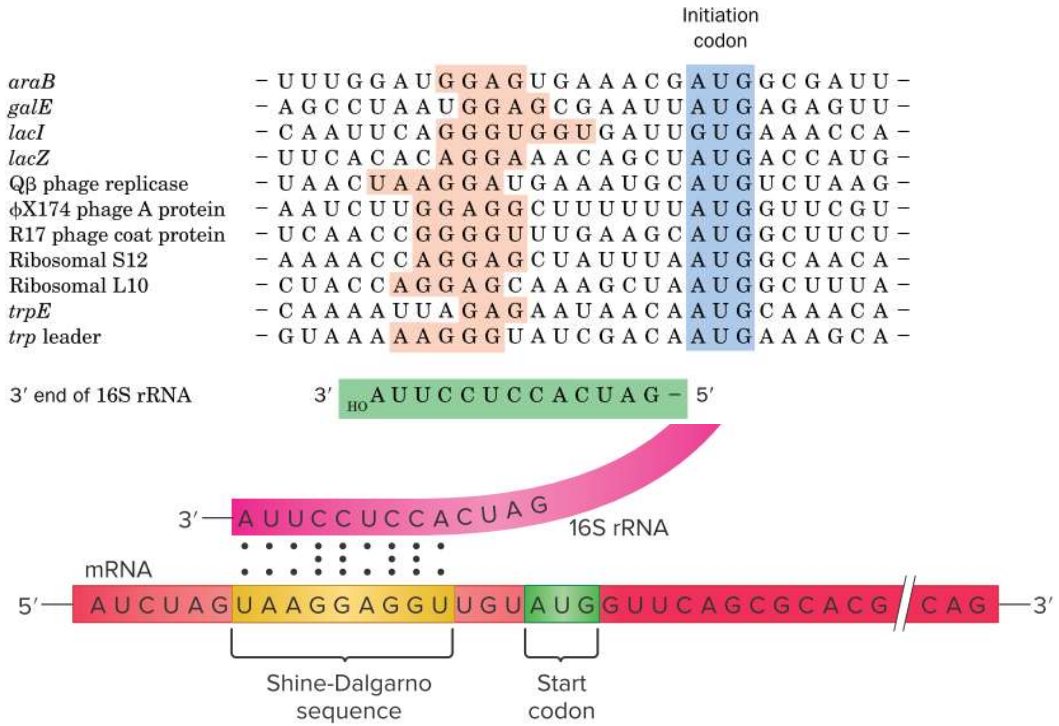


Overview of the stages of translation

Each initiator region usually displays an AUG codon. In addition, each initiator region contains a purine-rich sequence (called Shine–Dalgarno sequence) centered about 10 nucleotides on the 5′-side of the initiator codon. The 3′-end of 16s rRNA of the 30S subunit contains a sequence of several bases that is complementary to the purine-rich region in the initiator sites of mRNA. Thus, two kinds of interactions determine where protein synthesis starts:

(1) the pairing of mRNA bases with the 3′-end of 16S rRNA

(2) the pairing of the initiator codon on mRNA with the anticodon of an initiator tRNA molecule

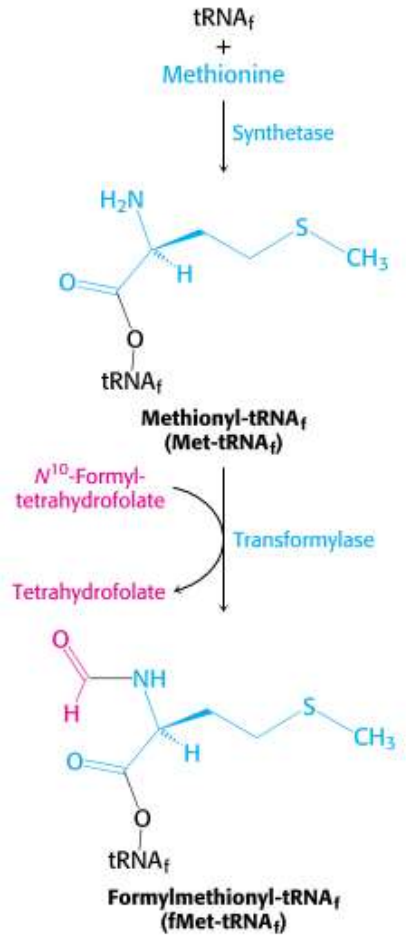


The locations of the Shine-Dalgarno sequence and the start codon in bacterial mRNA

Base-pairing interactions between an mRNA's Shine–Dalgarno sequence and the 16S rRNA apparently permit the ribosome to select the proper initiation codon. In addition, the 16S rRNA, which is a component of the small 30S ribosomal subunit, plays a key role by ensuring the proper recognition between the mRNA and the correct tRNA. The 16S rRNA can detect when an incorrect tRNA is bound at the A site and will prevent elongation until the mispaired tRNA is released from the A site. This phenomenon, termed the **decoding function of the ribosome**, is important in maintaining high fidelity of mRNA translation.

During initiation, an mRNA and the first tRNA bind to the ribosomal subunits. A specific tRNA functions as the initiator tRNA, which recognizes the start codon in the mRNA. In bacteria, the initiator tRNA, which is designated $tRNA^{fMet}$, carries a methionine that has been covalently modified to N-formylmethionine. In this modification, a formyl group (-CHO) is attached to the nitrogen atom in methionine after the methionine has been attached to the tRNA.

Formylation of methionyl-tRNA



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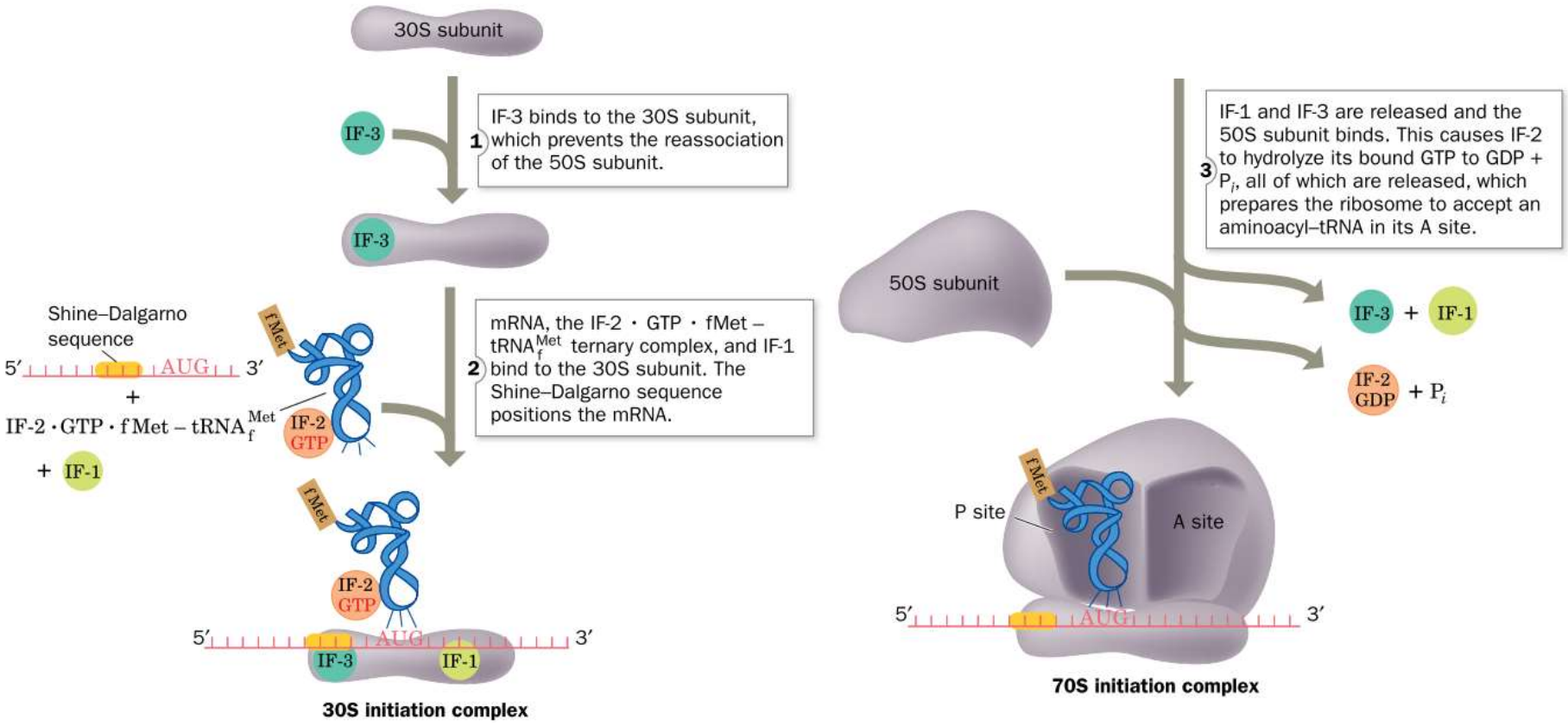
The initiation stage of translation in bacteria



Initiation results in the formation of an ***fMet–tRNA$_f^{Met}$ · mRNA · ribosome*** complex in which the *fMet–tRNA$_f^{Met}$* occupies the ribosome's P site while its A site is poised to accept an incoming aa–tRNA. The ***tRNA$_f^{Met}$*** is the only tRNA that directly enters the **P site**. All other tRNAs must first enter the A site during chain elongation.

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The initiation stage of translation in Eukaryotes

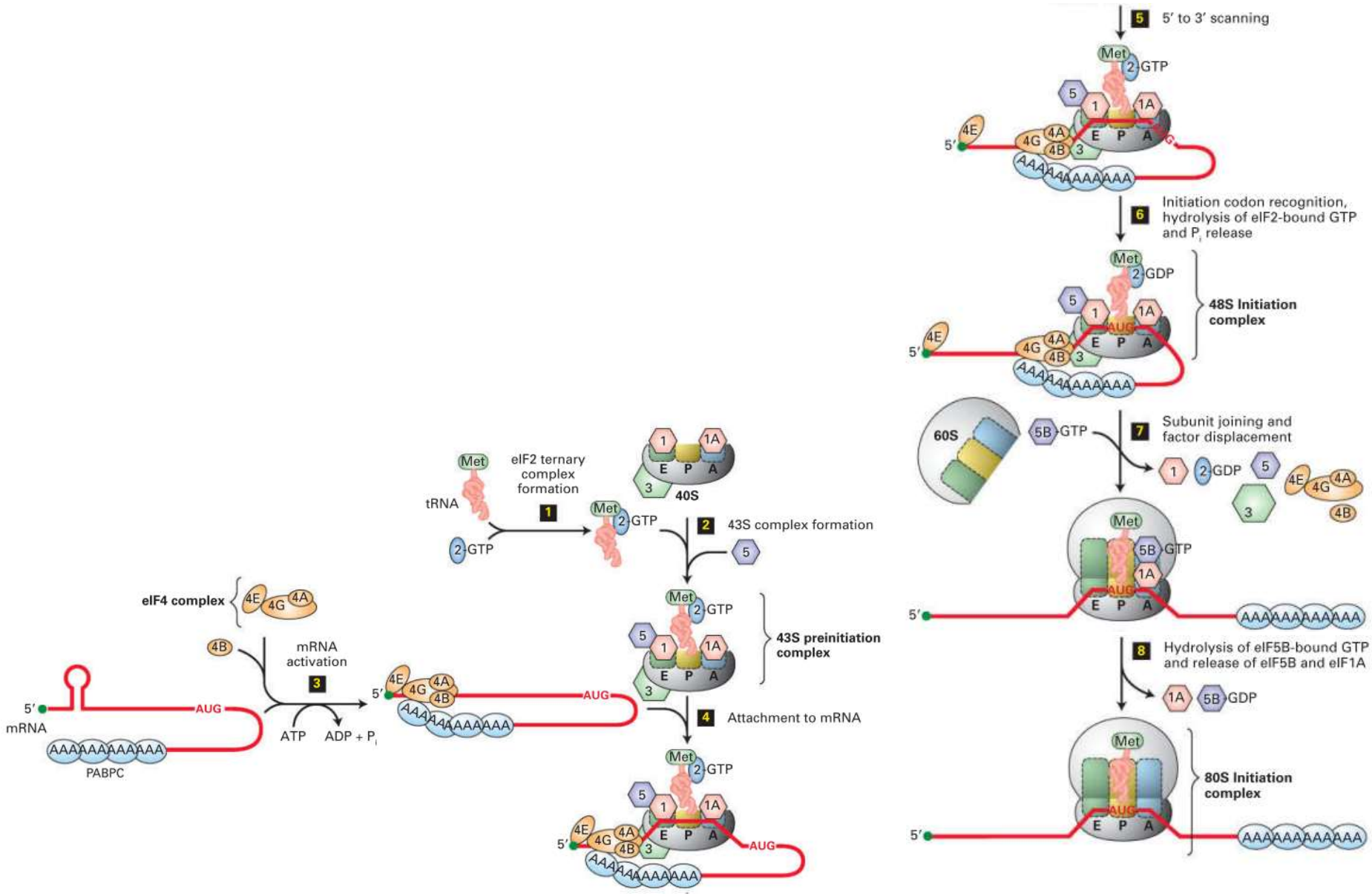
- The initiator tRNA in eukaryotes carries methionine rather than N-formylmethionine, as in bacteria.
- A eukaryotic initiation factor, eIF2 (for eukaryotic Initiation Factor), binds directly to $tRNA^{Met}$ to recruit it to the 40S subunit.
- The mRNA is recognized by eIF4, which is a multiprotein complex that recognizes the 7-methylguanosine cap at the 5′-end of the mRNA. eIF4 then facilitates the binding of the 5′ end of the mRNA to the 40S ribosomal subunit.
- After the initial binding of mRNA to the ribosome, the next step is locating an AUG start codon that is somewhere downstream from the 7-methylguanosine cap.
- In 1986, Marilyn Kozak proposed that the ribosome begins at the 5′ end and then scans along the mRNA in the 3′ direction in search of an AUG start codon. When a start codon is identified, eIF5 causes the release of the other initiation factors, which enables the 60S subunit to associate with the 40S subunit.
- Researchers have found that not all AUG codons near the 5′ end of mRNA can function as start codons. In some cases, the scanning ribosome passes over the first AUG codon and chooses an AUG farther down the mRNA.

The sequence of bases around the AUG codon plays an important role in determining whether or not it is selected as the start codon by a scanning ribosome. The consensus sequence for optimal start codon recognition in complex eukaryotes, such as vertebrates and vascular plants, is as follows:

						Start Codon			
G	C	C	(A/G)	C	C	A	U	G	G
–6	–5	–4	–3	–2	–1	+1	+2	+3	+4

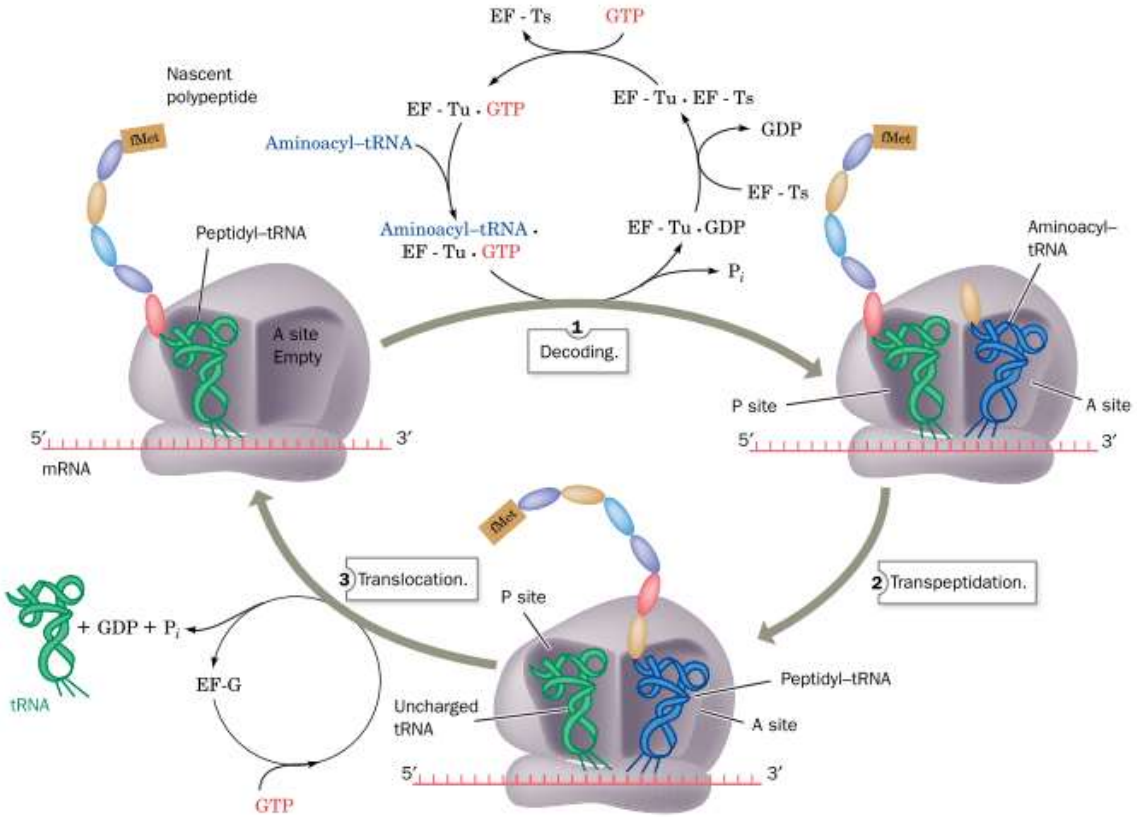
Aside from an AUG codon itself, a guanine at the +4 position and a purine, preferably an adenine, at the −3 position are the most important sites for start codon selection. These rules for optimal translation initiation are **called Kozak's rules**.

The initiation stage of translation in Eukaryotes



R. J. Jackson et al., 2010, Nature Rev. Mol. Cell Biol. 11:113.

Elongation cycle in *E. coli* ribosomes



The peptidyl transferase center that catalyzes peptide bond formation is located on the large subunit and consists entirely of rRNA.

1. **Decoding**, in which the ribosome selects and binds an aminoacyl–tRNA whose anticodon is complementary to the mRNA codon in the A site.
2. **Transpeptidation**, or peptide bond formation, in which the peptidyl group in the P-site tRNA is transferred to the aminoacyl group in the A site.
3. **Translocation**, in which the A-site and P-site tRNAs are respectively transferred to the P and E sites, accompanied by their bound mRNA; that is, the mRNA, together with its base-paired tRNAs, is ratcheted through the ribosome by one codon.

The role of GTP-hydrolyzing proteins in ribosome cycles

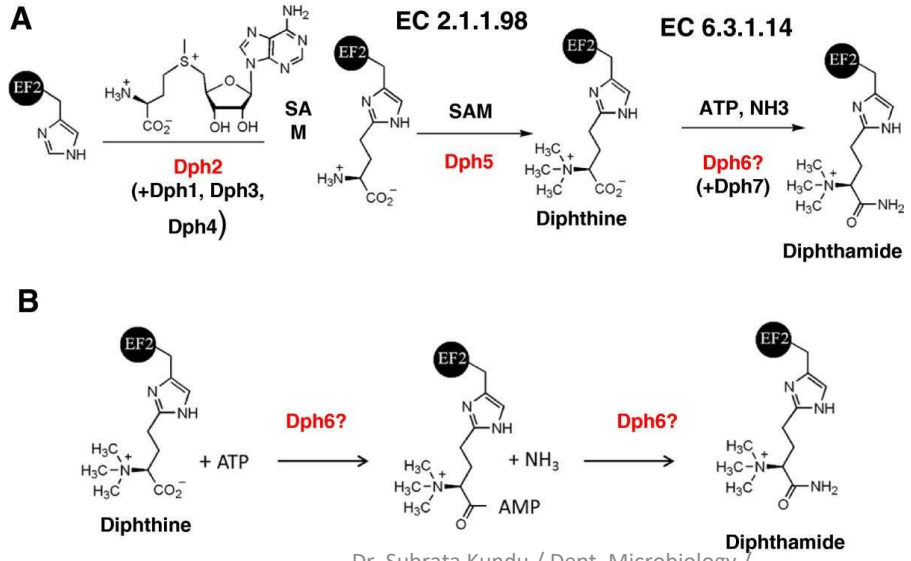
The requirement that the GTP-hydrolyzing proteins EF-Tu and EF-G alternate in their activities ensures that the ribosome cycles unidirectionally through the transpeptidation and translocation stages of translation. Translocation can occur in the absence of GTP, which indicates that the free energy of the transpeptidation reaction is sufficient to drive the entire translational process (this is a further indication that the primordial ribosome consisted only of RNA). However, the GTP hydrolysis catalyzed by EF-Tu and EF-G greatly increases the overall rate of translation, presumably by reducing the activation barriers between successive states. Because GTP hydrolysis is irreversible, the accompanying conformational changes in the ribosome are also irreversible and hence unidirectional.

The Eukaryotic Elongation Cycle Resembles That of Prokaryotes

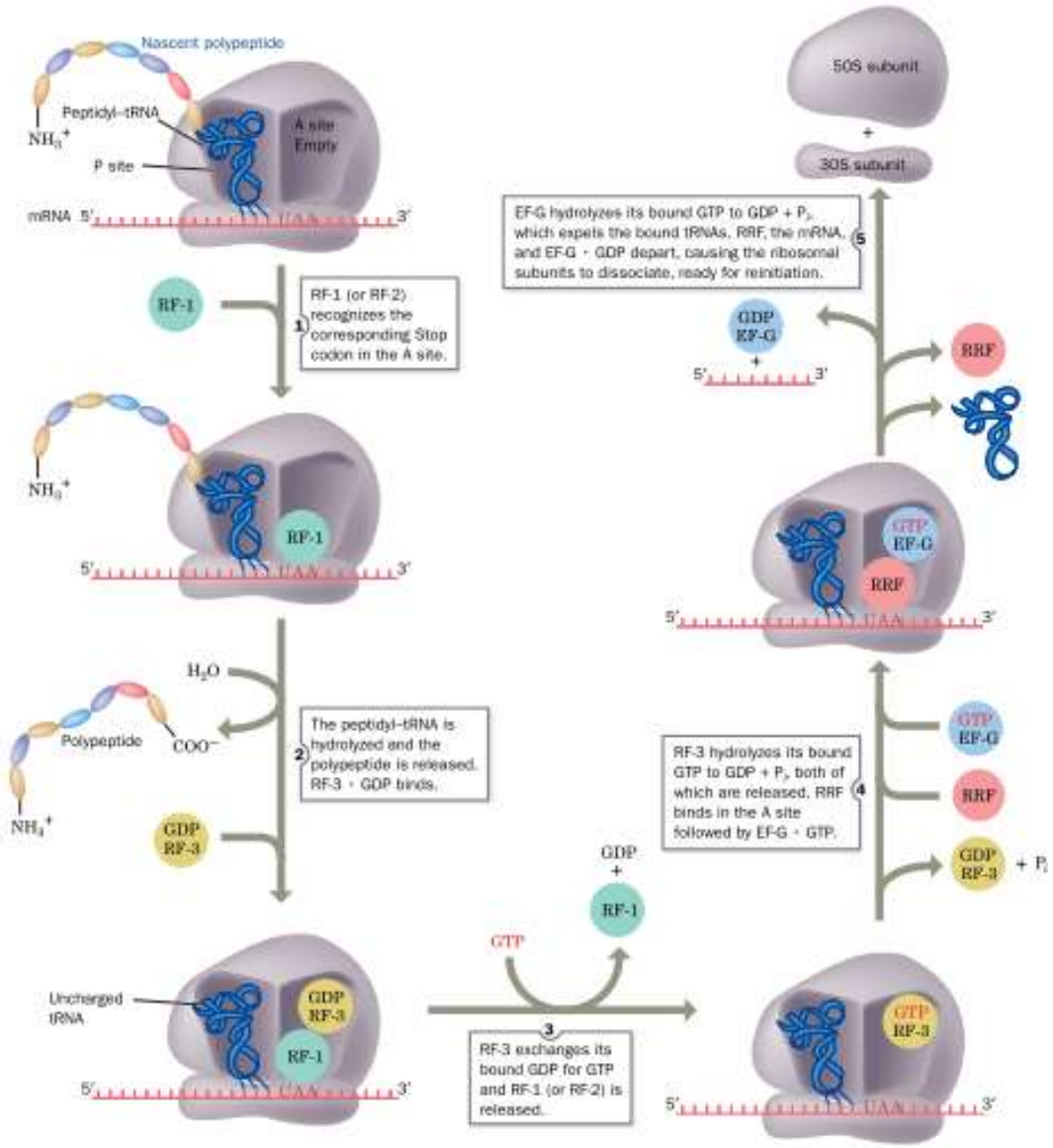
Elongation in eukaryotes closely resembles that in prokaryotes. In eukaryotes, the functions of EF-Tu and EF-Ts are assumed by the eukaryotic elongation factors eEF1A and eEF1B. Likewise, eEF2 functions in a manner analogous to prokaryotic EF-G.

- Archaeal and eukaryotic EF-2s contain a posttranslationally modified amino acid which is synthesized upon the addition of a 3-amino-3-carboxypropyl (ACP) group to a conserved histidine residue and its subsequent modification to diphthamide by the concerted action of three (in archaea) to seven enzymes (in eukaryotes). Its name refers to the target function for diphtheria toxin, the disease-causing agent that, through ADP ribosylation of diphthamide, causes irreversible inactivation of EF2 and cell death.

- Diphthamide interacts directly with codon–anticodon bases in the translating ribosome, and facilitates translation by displacing ribosomal decoding bases. In addition, diphthamide has been proposed to play a role in the regulation of translation, as it represents a site for reversible endogenous ADP-ribosylation and in the selective translation of certain genes in response to cellular stress



The translation termination pathway



The stop codons are recognized by proteins known as release factors. Interestingly, the three-dimensional structures of release factor proteins are "molecular mimics" that resemble the structure of tRNAs. Release factors can specifically bind to a stop codon sequence.

In bacteria, RF1 recognizes UAA and UAG, and RF2 recognizes UAA and UGA. A third release factor, RF3, is also required.

In eukaryotes, a single release factor, eRF1, recognizes all three stop codons, and eRF3 is also required for termination.

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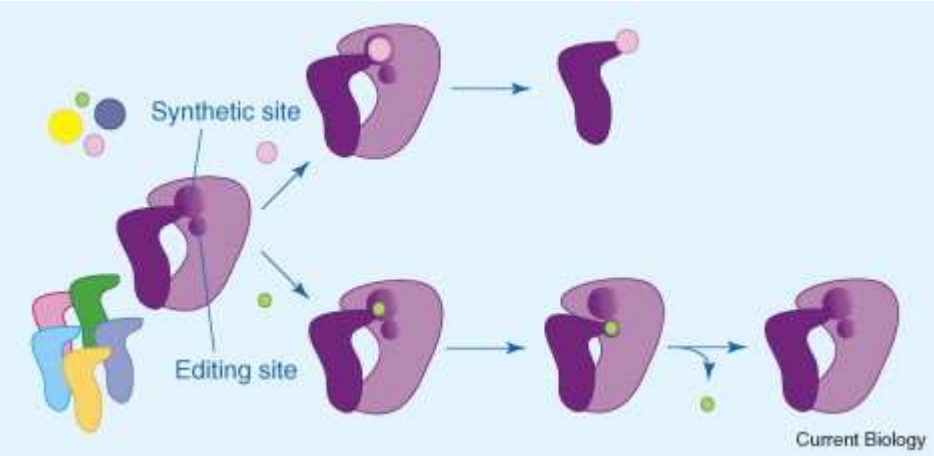
Fidelity of translation

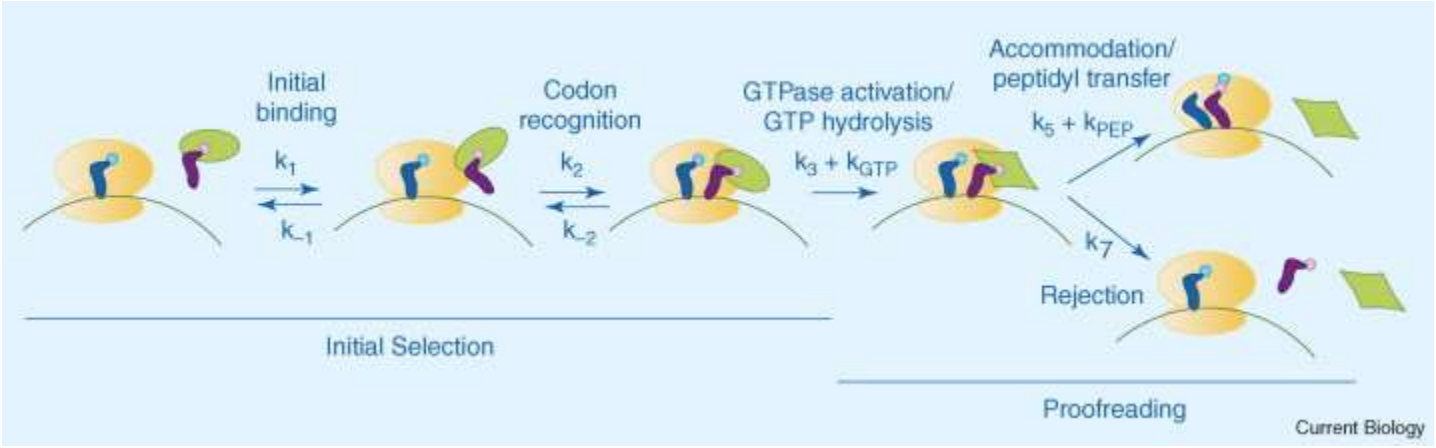
Protein synthesis or translation has an observed fidelity of 1 error in 10^3–10^4 polymerized amino acids. The following mechanisms are used to maintain the high fidelity of protein synthesis:

Editing activity of Aminoacyl-tRNA synthetases: The aminoacylation reaction, which takes place at a site of the enzyme called the synthetic site, occurs in two steps. First the amino acid is activated by adenylation (consuming ATP) and then it is transferred to the tRNA (releasing AMP). Steric exclusion of amino acids with larger side-chains and recognition of specific properties of each amino acid generally make this synthetic site specific enough so that only the correct amino acid can be activated and transferred. In addition, there are existence of second active site, called the **editing site**, where misactivated amino acids or misacylated tRNAs are hydrolyzed.



Editing mechanism involved in determining fidelity during tRNA aminoacylation.

Kinetic proofreading during tRNA selection: The difference in free energy of binding between the cognate and a non-cognate aminoacyl-tRNA (with two or three mismatches to the codon in the mRNA) is large enough to exclude the non-cognate aminoacyl-tRNA from the ribosome.



Detailed kinetic scheme for tRNA selection highlighting the two stages of the process, initial selection and proofreading.

The selectivity of the initial selection stage is determined by the difference in rate of GTPase activation (k_3) between the cognate and a near-cognate tRNA. The selectivity of the proofreading stage is determined primarily by the difference in rate of accommodation (k_5) between the cognate and a near-cognate tRNA. EF-Tu (green) is shown in two different conformations before and after GTP hydrolysis.

A Simplified Comparison of Translational Protein Factors in Bacteria and Eukaryotes

Bacterial Factors	Eukaryotic Factors*	Function
Initiation Factors		
	eIF4	Recognizes the 7-methylguanosine cap at the 5′-end of mRNA and facilitates the binding of the mRNA to the small ribosomal subunit
IF1, IF3	eIF1, eIF3, eIF6	Prevent the association between the small and large ribosomal subunits and favor their dissociation
IF2	eIF2	Promotes the binding of the initiator tRNA to the small ribosomal subunit
	eIF5	Helps to dissociate the initiation factors, which allows the two ribosomal subunits to assemble
Elongation Factors		
EF-Tu	eEF1α	Involved in the binding of tRNAs to the A site
EF-Ts	eEF1βγ	Nucleotide exchange factors required for the functioning of EF-Tu and eEF1α, respectively
EF-G	eEF2	Required for translocation
Release Factors		
RF1, RF2	eRF1	Recognize a stop codon and trigger the cleavage of the polypeptide from the tRNA
RF3	eRF3	GTPases that are also involved in termination

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A Comparison of Bacterial and Eukaryotic Translation

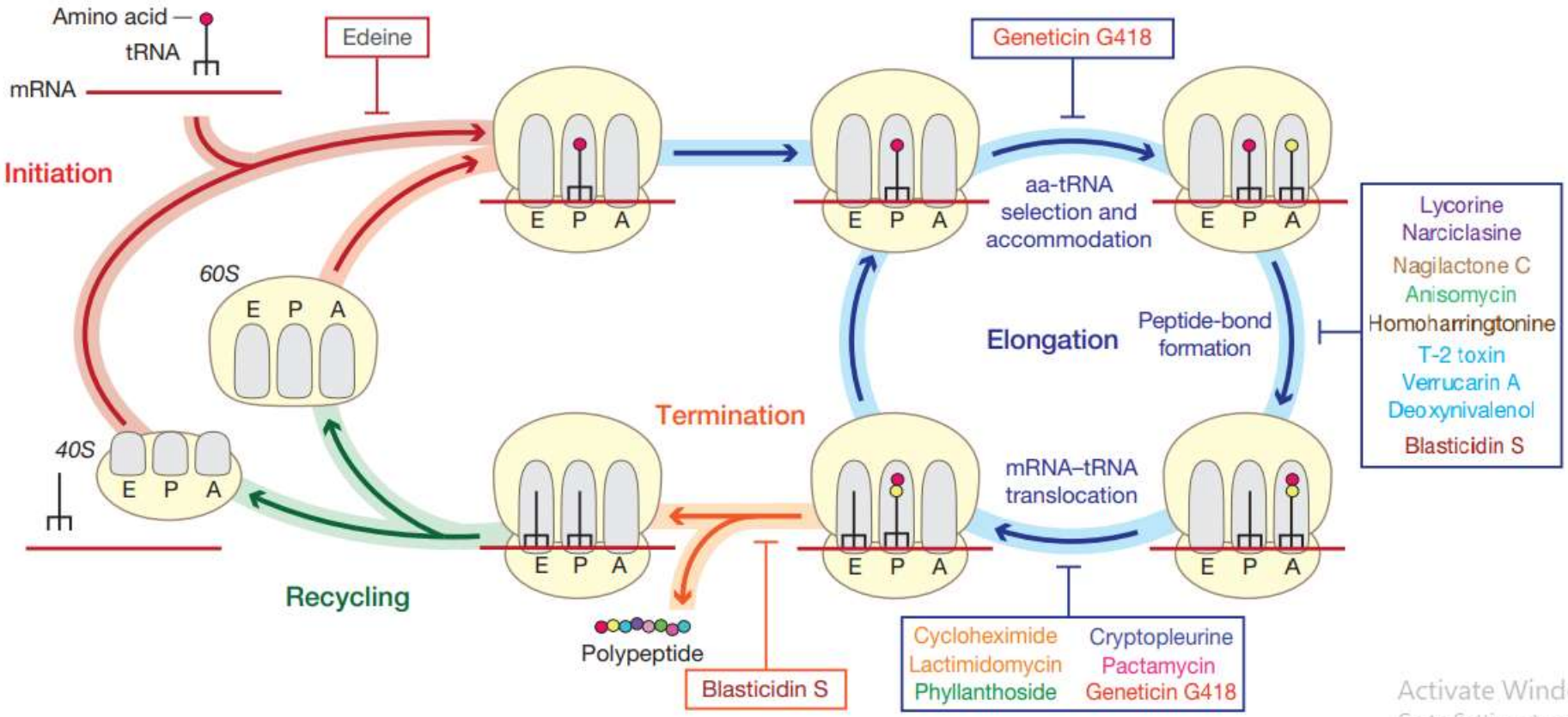
	Bacterial	Eukaryotic
Ribosome composition:	70S ribosomes: 30S subunit— 21 proteins + 1 rRNA 50S subunit— 34 proteins + 2 rRNAs	80S ribosomes: 40S subunit— 33 proteins + 1 rRNA 60S subunit— 49 proteins + 3 rRNAs
Initiator tRNA:	$tRNA^{fmet}$	$tRNA^{Met}$
Formation of the initiation complex:	Requires IF1, IF2, and IF3	Requires more initiation factors compared to bacterial initiation
Initial binding of mRNA to the ribosome:	Requires a Shine-Dalgarno sequence	Requires a 7-methylguanosine cap
Selection of a start codon:	AUG, GUG, or UUG located just downstream from the Shine-Dalgarno sequence	According to Kozak's rules
Elongation rate:	Typically 15–20 amino acids per second	Typically 2–6 amino acids per second
Termination:	Requires RF1, RF2, and RF3	Requires eRF1 and eRF3
Location of translation:	Cytoplasm	Cytosol
Coupled to transcription:	Yes	No

Mechanisms of Inhibition of Bacterial Translation via Selected Antibiotics

Antibiotic	Description
Chloraphenical	Blocks elongation by acting as competitive inhibitor of peptidyl transferase.
Erythromycin	Binds to the 23S RNA and blocks elongation by interfering with the translocation step.
Puromycin	Binds to the A site and causes premature release of the polypeptide. This early termination of translation results in polypeptides that are shorter than normal.
Tetracycline	Blocks elongation by inhibiting the binding of aminoacyl-tRNAs to the ribosome.
Streptomycin	Interferes with normal pairing between aminoacyl-tRNAs and codons. This causes misreading, thereby producing abnormal proteins.

Antibiotic	Action
Streptomycin and other aminoglycosides	Inhibit initiation and cause the misreading of mRNA (bacteria)
Tetracycline	Binds to the 30S subunit and inhibits the binding of aminoacyl-tRNAs (bacteria)
Chloramphenicol	Inhibits the peptidyl transferase activity of the 50S ribosomal subunit (bacteria)
Cycloheximide	Inhibits translocation (eukaryotes)
Erythromycin	Binds to the 50S subunit and inhibits translocation (bacteria)
Puromycin	Causes premature chain termination by acting as an analog of aminoacyl-tRNA (bacteria and eukaryotes)

Inhibitors action during protein synthesis in eukaryotes



Inhibitors action during protein synthesis in eukaryotes

- **Cycloheximide** is a **protein synthesis inhibitor** in eukaryotes. Although its precise mechanism of action has yet to be fully elucidated, it has been shown to **inhibit** translation elongation through binding to the E-site of the 60S ribosomal unit.

- **The broad-spectrum inhibitor blasticidin S target the peptidyl transferase centre on the large subunit. It** bound to the 60S tRNA P-site and efficiently inhibits peptide release mediated by release factor RF1 during termination of protein synthesis.

- Edeine has been shown to specifically inhibit binding of aminoacyl-tRNAs to the P site of eukaryotic 40S subunits.