

Decoding and Recoding of mRNA Sequences by the Ribosome

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Keywords

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Abstract

Faithful translation of messenger RNA (mRNA) into protein is essential to maintain protein homeostasis in the cell. Spontaneous translation errors are very rare due to stringent selection of cognate aminoacyl transfer RNAs (tRNAs) and the tight control of the mRNA reading frame by the ribosome. Recoding events, such as stop codon readthrough, frameshifting, and translational bypassing, reprogram the ribosome to make intentional mistakes and produce alternative proteins from the same mRNA. The hallmark of recoding is the change of ribosome dynamics. The signals for recoding are built into the mRNA, but their reading depends on the genetic makeup of the cell, resulting in cell-specific changes in expression programs. In this review, I discuss the mechanisms of canonical decoding and tRNA–mRNA translocation; describe alternative pathways leading to recoding; and identify the links among mRNA signals, ribosome dynamics, and recoding.

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INTRODUCTION

The ribosome is a molecular machine that translates the nucleotide sequence of messenger RNAs (mRNAs) into the amino acid sequence of proteins. Translation of each mRNA entails initiation, elongation, and termination phases, with subsequent ribosome and mRNA recycling. One remarkable feature of the ribosome is its high fidelity, which accounts for the low frequency of missense, nonsense, and frameshifting errors and ensures the synthesis of functional proteins. The ribosome also contributes to accurate protein folding, as nascent peptides start to fold cotranslationally inside the peptide exit tunnel or close to the surface of the ribosome. While the ribosome has evolved sophisticated mechanisms to avoid translation errors at the decoding and translocation phases of translation elongation (**Figure 1**) and to help in nascent protein folding, signals in

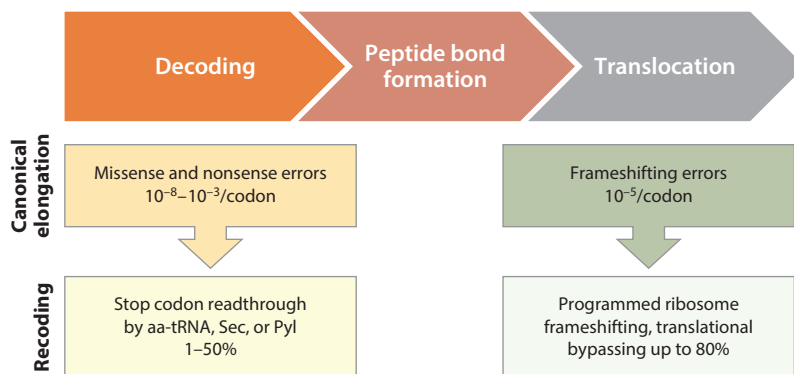


Figure 1

Decoding and recoding. The translation elongation cycle entails decoding, peptide bond formation, and tRNA–mRNA translocation. The high fidelity of decoding is ensured by an induced-fit mechanism governed by the correct codon–anticodon base pairing in the A site (91, 101, 102). Peptide bond formation contributes to the decoding fidelity by making the choice of aa-tRNA irreversible. Post-peptide-bond editing of incorrect peptidyl-tRNAs results in termination of translation (140). Translocation ensures accurate reading frame maintenance. Recoding alleviates fidelity control mechanisms and results in efficient stop codon readthrough, frameshifting, or bypassing. Abbreviations: aa-tRNA, aminoacyl-tRNA; mRNA, messenger RNA; tRNA, transfer RNA.

the mRNA can reprogram the ribosome to make intentional mistakes, which leads to recoding of the genetic information and enriches the protein repertoire of the cell. The recoding signals are built into the mRNA beyond the information on the amino acid encoded and can be encoded as secondary structure elements of the mRNA, evolutionary conserved codon choice, or sequences inducing ribosome stalling.

Recoding signals can change translation fidelity dramatically (**Figure 1**). The frequency of misreading errors, which is normally in the range of 10^{-8} – 10^{-3} per codon, increases to approximately 50% when the ribosome encounters a stop codon designated for recoding by selenocysteine and is in the range of a few percent in cases of programmed translational readthrough. Frameshifting errors are usually very infrequent, in the range of 10^{-5} per codon, but specific signals for programmed ribosome frameshifting can increase slippage efficiency up to 80%. A combination of mRNA secondary structures with the interactions of nascent peptide with the peptide exit tunnel of the ribosome can result in the ribosome skipping 50 nucleotides of the coding sequences to synthesize a single protein from a discontinuous mRNA sequence. The purpose of this review is to show how the mechanisms that maintain high fidelity of translation elongation are altered by recoding signals and to explore the importance of ribosome dynamics in switching between decoding and recoding programs.

DECODING

Translation Fidelity

Missense errors result from incorrect reading of a sense codon during the decoding step of translation elongation. Such errors can arise due to charging of a transfer RNA (tRNA) with an incorrect amino acid or misreading of an mRNA codon by an incorrect aminoacyl-tRNA (aa-tRNA) on the ribosome. Because errors are rare, it is not easy to estimate their frequency with confidence. Early reports that examined error frequencies in a few selected proteins suggested an error frequency of approximately 10^{-5} – 10^{-3} , which remains the most cited (and rather overestimated) value in the literature. Measurements based on reporter systems suggest that most errors are very infrequent (70, 74, 80, 113, 121, 125). The recent development of mass spectrometry methods estimates the error frequency in a more systematic way, showing that the *in vivo* steady-state missense error level is very low, with most errors ranging from 10^{-7} to 10^{-5} , with a few hotspots of 10^{-4} – 10^{-3} , depending on the type of mismatches in the codon–anticodon complex (42, 81, 136, 141). Analysis of the error hotspots suggests that G–U mismatches, in particular in the second codon position, are tolerated better than other mismatches, causing increased error frequency (10^{-3}) (42, 136). This tendency is conserved between bacteria and yeast (81) and likely reflects the formation of rare tautomeric forms that have geometry identical to the Watson–Crick base pairing, which precludes their discrimination by the ribosome (110). This implies that other base pairs prone to tautomerization may lead to high error frequencies, but these occurrences are surprisingly rare. Another source of unconventional base pairs that mimic Watson–Crick geometry is chemical modifications (108), which are prevalent in tRNA anticodons (122) and also found in mRNAs (99).

Surprisingly, the analysis of error frequencies in different proteins and along the sequence of a protein reveals a nonrandom distribution of errors, with some proteins and even regions of proteins being more error prone than others for the same type of amino acid substitutions. Why this is so is unclear. Translational efficiency of the given mRNA plays a role: There are fewer errors when ribosomes translate naturally highly expressed genes (81), whereas overexpression leads to more errors (42). The observed fidelity also changes under conditions of cellular stress, e.g., due to amino acid depletion or in the presence of antibiotics, which results in the accumulation of

misfolded proteins. In this respect, it is important to note that the steady-state error frequencies measured by mass spectrometry are the result of the interplay of several machineries, including transcription and translation that make mistakes and the quality control machineries that destroy aberrant protein products. Transcription error frequencies range between 10^{-6} and 5×10^{-5} independent of growth conditions and sequence context (27, 127), which is somewhat surprising given that translational error frequencies seem to be lower. This comparison would imply a large contribution of cellular proteases in degrading aberrant proteins, and, in fact, the error frequency is higher in a strain lacking the Lon protease (81). Given the role of the quality control machinery in recognition of misfolded proteins (27, 46, 47), it is also possible that, even for the same type of mismatch, proteins with errors in critical positions will be preferentially removed, which would reduce the steady-state error rate.

One recently discovered type of error is error clusters resulting from the accumulation of several consecutive errors upon treatment with aminoglycoside antibiotics (136). Remarkably, only the first error in the error cluster has a low frequency, $<10^{-3}$, whereas all of the following misreading events are extremely efficient, with 20–40% ribosomes incorporating a wrong amino acid. This is because the first error depends on many processes, such as the probabilities that the antibiotic enters the cell and that it binds to the ribosome. In contrast, subsequent errors occur when the antibiotic is already bound, reflecting an intrinsic propensity of the antibiotic-bound ribosome to make mistakes. Error accumulation is likely to produce misfolded or poorly functional proteins. Errors in membrane proteins might impair the ability of the cell to prevent antibiotic leakage into the cell and the activity of the efflux pumps that remove the antibiotics out of the cell, which might favor further drug influx at early stages of antibiotic treatment (136).

The Mechanism of Decoding and Aminoacyl-Transfer RNA Selection

The ribosome translates the sequence of mRNA codons into amino acids in the proteins with the help of aa-tRNAs. aa-tRNAs are delivered to the ribosome by elongation factor Tu (EF-Tu), a GTPase that in its GTP-bound form binds aa-tRNAs. The ribosome selects aa-tRNAs according to the match between the anticodon of aa-tRNA and the codon presented in the decoding site of the small ribosomal subunit (SSU). Different ternary complexes of EF-Tu–GTP–aa-tRNA (cognate, near-cognate, and noncognate to the given codon) compete for binding. The ribosome monitors the quality of the codon–anticodon interaction and accepts those aa-tRNAs that have passed the discrimination steps of initial selection and proofreading (**Figure 2**).

The work on the mechanism of aa-tRNA selection has suggested that cognate aa-tRNAs are selected, and near- and noncognate aa-tRNAs are rejected due to the differences in their dissociation rates from the ribosome and the rates of forward reactions. The key selection steps are GTP hydrolysis by EF-Tu after codon recognition on the SSU and aa-tRNA accommodation in the A site; aa-tRNA accommodation entails binding of the tRNA CCA end in the A site of the peptidyl transferase center of the large ribosomal subunit (LSU) (for reviews, see 101, 102). Early structural work unraveled how the ribosome distinguishes correct and incorrect substrates (88, 98). Recently, cryo-electron microscopy (cryo-EM) structures demonstrated how EF-Tu–GTP–aa-tRNA (72, 73) and a specialized ternary complex of EF-Tu homolog SelB specializing in delivery of a single aa-tRNA, Sec-tRNA^{Sec} (37), rearrange upon codon recognition and accommodation. Crystallography provided snapshots of several codon–anticodon complexes revealing the roles of tautomerization and tRNA modifications in recognition (106, 107, 109). Computer simulations play an important role in reconstructing the pathways that cannot be viewed by cryo-EM (114). Finally, rapid kinetics and single-molecule studies provide information about the sequence of events, the dynamics, and the effective rates of the individual steps, which together show how decoding

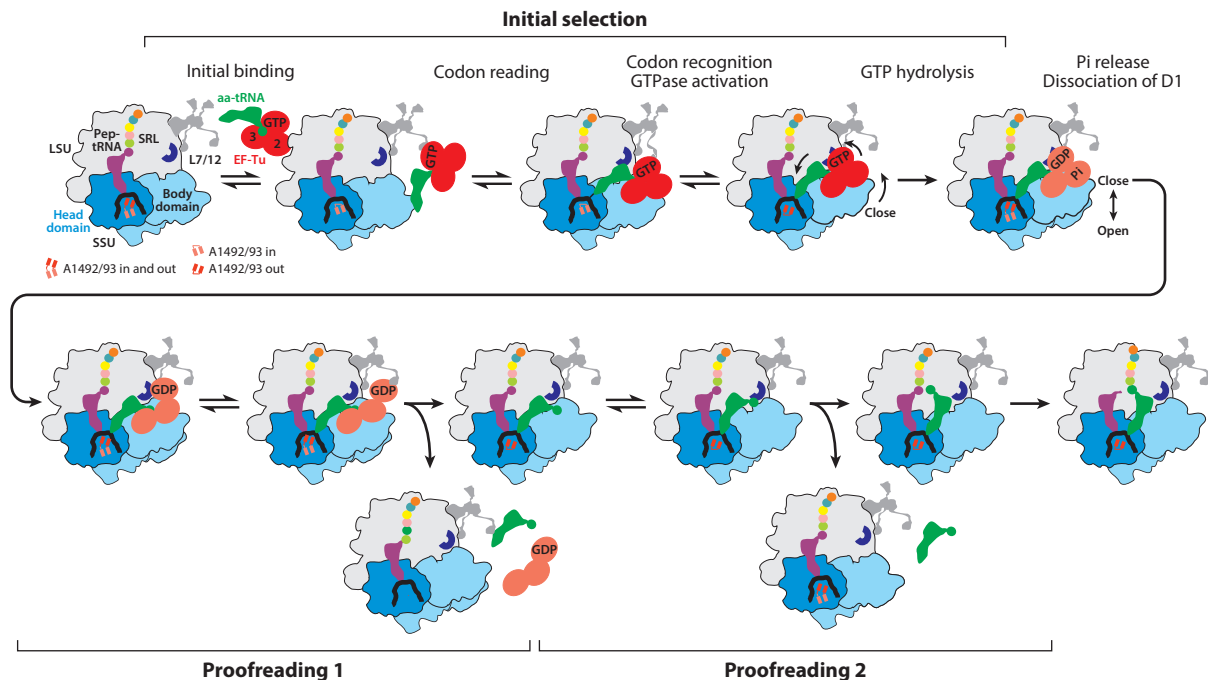


Figure 2

The mechanism of decoding. Initial binding is codon independent, whereas subsequent codon reading entails partial codon–anticodon interactions. The rest of the scheme shows the mechanism for the cognate aa-tRNA that induces the local rearrangement of A1492/93 and the SSU domain closure upon codon recognition (indicated by arrows). Docking of EF-Tu domain 1 on the SRL induces rapid GTP hydrolysis. Near-cognate aa-tRNA does not induce the domain closure and tends to dissociate rather than dock to the SRL, which explains the low rate of GTP hydrolysis and contributes to the fidelity of the initial selection phase. Pi release remodels the switch regions of the GTPase, initiating the release of aa-tRNA sequentially starting with domain 1, then 2, then 3. Near-cognate aa-tRNA can be rejected in the complex with EF-Tu-GDP (or GDP-Pi) (proofreading 1) or after dissociation of EF-Tu (proofreading 2). Abbreviations: aa-tRNA, aminoacyl-transfer RNA; EF-Tu, elongation factor Tu; LSU, large ribosomal subunit; SRL, sarcin-ricin loop; SSU, small ribosomal subunit.

and aa-tRNA selection work. Given that single-molecule and rapid kinetics aspects have been reviewed recently (18, 91, 102), below I provide an integrated view of decoding with an emphasis on recent findings.

The initial binding of EF-Tu–GTP–aa-tRNA to the ribosome does not involve codon recognition and is mediated by interactions of EF-Tu with ribosomal protein uL12 of the LSU (26, 69) (**Figure 2**). In this early complex, EF-Tu is separated from the GTPase-activating center of the ribosome, the sarcin-ricin loop (SRL) of the LSU, and can even be protected by the interactions with the aa-tRNA in the ternary complex (37). From this position in the complex, aa-tRNA attempts to read the codon by establishing stepwise base-pair interaction (37, 72). Formation of a fully matched codon–anticodon complex with correct Watson-Crick geometry at the first and second codon positions triggers a sequence of events that results in the selection of the aa-tRNA as cognate for the recruitment to the A site. The SSU 16S ribosomal RNA (rRNA) residues A1492 and A1493 at the decoding site of the ribosome form A-minor interactions with the codon–anticodon duplex and, with the help of G530 and ribosomal protein uS12, form a network of interactions that recognizes the geometry of Watson-Crick base pairs (88). These local rearrangements induce a movement of the head domain of the SSU toward the shoulder of the SSU body, which results in

the domain closure on the correct codon–anticodon complex. SSU domain closure moves EF-Tu from its outside docking position onto the SRL (37, 72) and results in bending and distortions of aa-tRNA (117, 130). Docking of EF-Tu at the SRL assembles the composite GTPase center, thereby triggering rapid GTP hydrolysis (78). A near-cognate aa-tRNA that does not form a perfect Watson–Crick interaction fails to induce the local rearrangement and the global domain closure (37, 72). This results in a much lower GTPase activation and does not stabilize the aa-tRNA, resulting in its rejection (101, 102). Cryo-EM and single-molecule Förster resonance energy transfer (smFRET) data suggest that domain closure is reversible at this stage, even with a cognate aa-tRNA (43, 73). Notably, while the fluctuations at the initial selection phase are conceivably important for the rejection of near-cognate aa-tRNAs, they are unlikely to play a role for the cognate aa-tRNA binding due to the rapid GTP hydrolysis that occurs as soon as EF-Tu has docked on the SRL (78).

After GTP hydrolysis, aa-tRNA remains bound to EF-Tu for some time due to delayed release of the reaction product inorganic phosphate (Pi) (68). Biochemical data, computer simulations, and cryo-EM structures suggest that the length of the Pi-bound stage, as well as the time required for EF-Tu to release aa-tRNA, defines a time window during which aa-tRNA can dissociate from the ribosome while still attached to EF-Tu (57, 73, 87, 100). Structural studies suggest that the ribosome continues its fluctuations from the open to the closed conformation and that these fluctuations stop only upon EF-Tu dissociation (73). The efficiency of proofreading prior to aa-tRNA and EF-Tu separation seems to be in the range of 10 to 50, very similar to that for aa-tRNA accommodation after EF-Tu release (57). While this now emerges as an important additional selection branch during proofreading, in earlier models, this step was included in the collective proofreading efficiency of all steps after GTP hydrolysis.

Cryo-EM and computer simulations suggested a stepwise dissociation of EF-Tu from aa-tRNA and the ribosome starting with the G-domain (domain 1), followed by domain 2 and domain 3 (73, 132). As in all members of the GTPase superfamily, the rearrangement of EF-Tu from the compact GTP-bound to the extended GDP-like form is triggered by the rearrangement of the switch 1 region in the G-domain. Upon Pi release, switch 1 adopts a β -hairpin structure that is incompatible with aa-tRNA binding (73), promoting aa-tRNA release from the G-domain. The distortion of aa-tRNA in the complex with ribosome-bound EF-Tu (130) also facilitates thermally driven excursions of the aa-tRNA elbow away from EF-Tu–GDP, which may facilitate aa-tRNA dissociation from domain 2 (82). Further relaxation of aa-tRNA upon its movement toward the accommodation corridor probably disrupts the remaining interactions with domain 3. In view of the structural data, a power-stroke-like mechanism by which EF-Tu propels aa-tRNA into the A site (87) seems unlikely.

The trajectory of aa-tRNA accommodation leads through the narrow space between the ribosomal subunits, 80 Å away from its binding site on EF-Tu to the A site in the peptidyl transferase center (PTC). Early molecular dynamics simulations have shown that LSU 23S rRNA helices (denoted as H)—most notably H89 (residues 2454–2498) and the A loop (H92)—occlude the tRNA path (115). Accommodation involves reversible excursions of aa-tRNA along multiple pathways (134). Cryo-EM structures identified two distinct pathways for cognate aa-tRNA accommodation (73). In pathway 1, the aa-tRNA elbow region moves first, followed by the movement of the CCA-arm into the A site of the PTC on the LSU. On its way, the elbow of aa-tRNA contacts the so-called A-site finger (ASF) (nucleotides 863–915 of H38 in 23S rRNA), whereas the acceptor arm contacts H89 and H92. With time, the CCA-arm passes H89, but H92 delays full accommodation of aa-tRNA in the A site (73). Alternatively, accommodation entails a rotation of the SSU by approximately 2.5° relative to the LSU, which moves both the ASF and H89 to enable the tRNA to bypass the occlusions. The latter pathway appears more favorable; however, it is

not clear whether one of them is favored at conditions of rapid translation (decoding at cryo-EM conditions was deliberately made slow to isolate the intermediates). A transient subunit rotation during accommodation has not been reported to date but could be tested using smFRET.

During accommodation of cognate aa-tRNA, the ribosome is found predominantly in the closed conformation (73), consistent with very slow aa-tRNA dissociation during accommodation (48). In contrast, when a near-cognate aa-tRNA attempts to traverse the accommodation corridor, the ribosome continues sampling the open conformation, and the accommodation pathway is perturbed (73). Sampling of the open 30S conformation explains the high rate of near-cognate tRNA release (48). Interestingly, even after accommodation, near-cognate aa-tRNA remains poorly positioned not only in the SSU decoding site, where the mismatch disturbs the codon–anticodon geometry, but also in the PTC of the LSU, which explains why the rate of peptidyl transfer is lower for the near-cognate, than for the cognate, substrate (48, 73). The mechanism of decoding provides a clear example of how the conformational dynamics of the ribosome contributes to high translational fidelity in response to geometric recognition of the Watson–Crick geometry of the codon–anticodon complex.

TRANSLOCATION

Mechanism of Translocation

After peptide bond formation, the ribosome moves by one codon along the mRNA in a process called translocation. Spontaneous translocation is very slow and—depending on the tRNAs—can be reversible (39, 64, 119). Elongation factor G (EF-G) is a translational GTPase that accelerates translocation at the cost of GTP hydrolysis. Translocation occurs precisely by one codon at a time, sometimes against hurdles of secondary structures in the mRNA. In this section, I summarize recent work that has shown how conformational changes of EF-G induced by GTP hydrolysis promote tRNA and mRNA movement and how EF-G helps the ribosome to maintain the reading frame on the mRNA.

In the pretranslocation (PRE) state, peptidyl-tRNA and deacylated tRNA occupy the A and P sites of the ribosome, respectively. The complex is dynamic, with the ribosomal subunits moving relative to each other (**Figure 3a**). The positions of the tRNA anticodons remain the same, but the tRNA CCA-arms move toward the P and E sites, respectively. At rates of approximately $1\text{--}40\text{ s}^{-1}$, depending on conditions, these fluctuations are relatively slow (20, 30, 34, 118, 131, 133). Binding of EF-G accelerates the transition to 200 s^{-1} (118) and stabilizes the rotated/hybrid (R/H) state. The elbow of the A/P-site tRNA makes additional excursions toward the P site; this state is denoted as A/P* (15, 95). Upon binding to the ribosome, EF-G adopts an elongated form spanning the interface between the SSU and LSU with its G-domain (D1) bound to the SRL and domain 4 (D4) oriented toward the decoding site of the SSU (12). The contact with the SRL triggers rapid ($>200\text{ s}^{-1}$) GTP hydrolysis by EF-G, but the release of the reaction product Pi is delayed (89, 104, 116).

Early kinetics measurements have shown that Pi release unlocks the tRNA movement on the SSU, which overcomes the major barrier on the translocation pathway (116). Recent time-resolved cryo-EM structures show how Pi release triggers translocation (15, 95, 112). The structure of the translocation intermediate after GTP hydrolysis but before the tRNAs move relative to the SSU reveals how GDP–Pi is coordinated in the nucleotide binding pocket of EF-G on the ribosome (15, 95) (**Figure 3b**). The key GTP sensor, the switch 1 region (sw1; *Escherichia coli* EF-G residues 32–65), adopts a compact structure that connects the SSU and LSU and stabilizes the ribosomal subunits in the rotated (R) state. The compact fold of sw1 is supported by a network of interactions with the Pi and switch 2 region (sw2; residues 86–105) of EF-G D1, the SRL of 23S rRNA

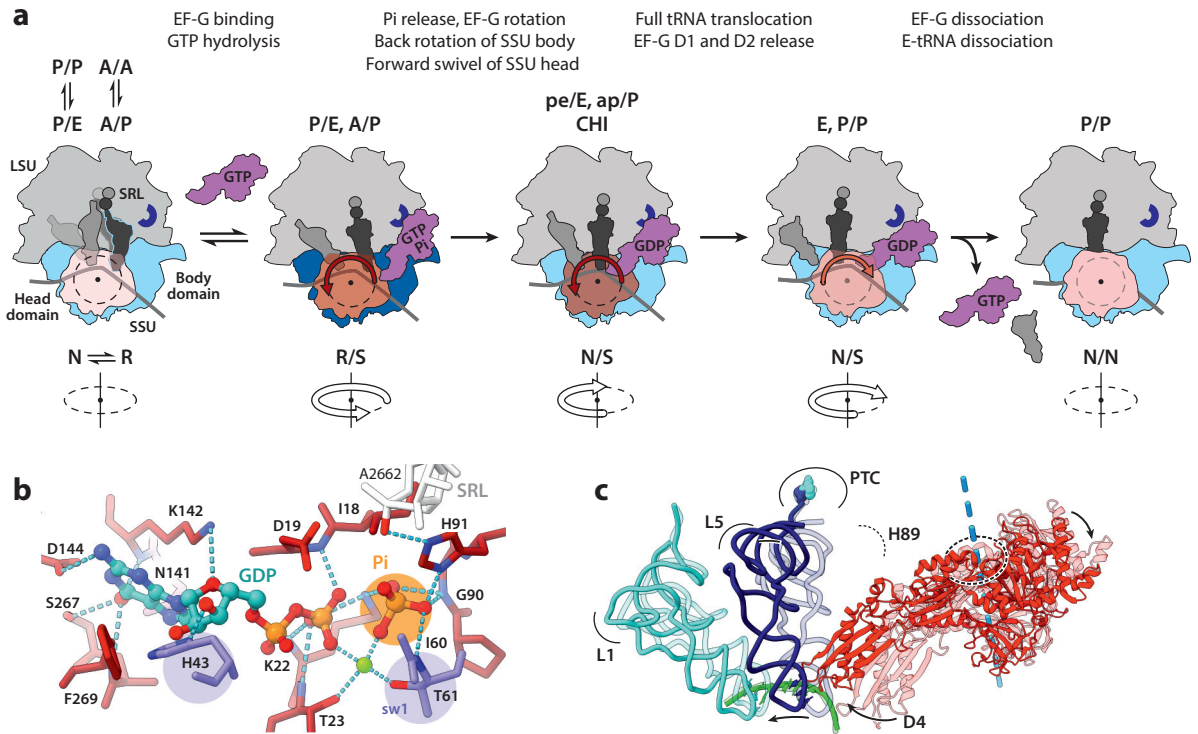


Figure 3

The mechanism of tRNA–mRNA translocation. (a) Prior to translocation, the PRE complex fluctuates between the nonrotated (N) orientation of the ribosomal subunits with tRNAs in classical states (A/A, P/P) and the rotated (R) orientation with tRNAs in hybrid A/P and P/E states (the tRNA fluctuations are shown in overlapping gray colors). Binding of EF-G–GTP accelerates the transition to the R state (indicated as a change of color from light to dark blue and by an arrow below the ribosome image) and stabilizes the tRNAs in their hybrid positions. The SSU head moves together with the body domain (change of color from light to dark pink and arrows in the SSU head schematic). GTP hydrolysis by EF-G is rapid, but Pi release is delayed. Pi release remodels the switch regions of EF-G, resulting in movement of the SSU body toward the N position, whereas the SSU head swivels forward (indicated by the darker color). The tRNAs move to intermediate ap/P and pe/E positions in the CHI state. Further steps entail full tRNA translocation to the P and E sites, stepwise dissociation of EF-G starting with D1 and D2, and backward swivel of the SSU head. In the final step, E-site tRNA and EF-G dissociate from the ribosome (6, 15, 95, 133, 142). (b) Coordination of GDP and Pi in ribosome-bound EF-G. Panel reproduced from Reference 95. (c) Conformational transition from the EF-G–GDP–Pi-bound state (*light colors*) to the CHI state (*dark colors*). In the EF-G–GDP–Pi state, EF-G D4 is flexible (95). After Pi release, EF-G rotates (the rotation axis is indicated), and D4 binds into the A site, where it contacts the tRNA and SSU. Positions of LSU elements L1, L5, and H89 and of the PTC are added for orientation. Panel reproduced from Reference 95. Abbreviations: CHI, chimeric; EF-G, elongation factor G; LSU, long ribosomal subunit; mRNA, messenger RNA; PRE, pretranslocation; PTC, peptidyltransferase center; SRL, sarcin–ricin loop; SSU, small ribosomal subunit; tRNA, transfer RNA.

on the LSU, and H14 of 16S rRNA in the SSU body domain. The SRL is found in a unique twisted conformation with its apical part (bases A2660–A2662) displaced by >2.5 Å compared to its position in other ribosome structures. EF-G D2 and D3 contact the SSU, whereas D4 points into the decoding center on the SSU but appears flexible, with its tip moving from H34 at the SSU head domain toward the A-site tRNA.

Pi release triggers a large-scale rotation of EF-G, global rearrangements of the ribosome, and tRNA movement on the SSU (15, 95) (**Figure 3c**). The loss of Pi coordination remodels the GTPase center. The entire sw1 moves away from the SRL and refolds from the compact to an extended conformation, which is stabilized by interactions with D2. The disruption of interactions

with sw1 and sw2 allows the SRL to relax into its ground state conformation. EF-G D1 and D5 remain docked on the apical part of the SRL and move together with the SRL, resulting in a large-scale rigid body rotation of EF-G toward the decoding center, where it contacts the A-site tRNA and the SSU. The conformation of the ribosome changes dramatically: The SSU body domain rotates backward relative to the LSU, whereas the SSU head domain continues the swiveling motion in a forward direction. EF-G D2 rolls over the SSU shoulder and stabilizes the back-rotated conformation of the SSU body domain; EF-G D3 accommodates the changes by shifting its contacts with the SSU. The tRNAs move from H into chimeric (CHI) states, where the tRNA anticodons shift together with the mRNA relative to the SSU body domain while remaining in contact with the SSU head domain, whereas on the LSU the CCA ends stay in the P and E sites, thereby forming ap/P and pe/E states. EF-G D4 swings into the decoding center, where it interacts with the tRNA–mRNA complex, the LSU, and the SSU head domain. In the CHI state, EF-G D4 is tightly bound to the decoding center, but D1 and D2 become more dynamic, indicating the direction of EF-G rearrangements when tRNAs move from the CHI to the posttranslocation (POST) state. The CHI state is a key intermediate of translocation. Its position on the translocation trajectory is supported by the structural work of several groups, as well as by smFRET and rapid kinetics measurements (1, 6, 15, 89, 95, 133, 142). In addition, the sequence and timing of SSU domain movements and tRNA–mRNA translocation are supported by kinetics data (6), providing a consistent model for the early stages of translocation from EF-G binding to the formation of the CHI state.

The later stages of translocation are less well understood. Cryo-EM data suggest that further progression of the tRNAs toward the P and E sites on the SSU initiate dissociation of EF-G D1 and D2 (15). Kinetics data indicate that, after the completion of tRNA translocation, the SSU head domain swivels backward, and this motion is completed with the final dissociation of EF-G–GDP and of the deacylated tRNA from the E site (6) (**Figure 3a**). Additional movements of the SSU head domain, such as tilting or hyperswiveling, are also possible (84, 86, 133).

While most of the data available so far are consistent with the model in **Figure 3a**, some questions remain. One question concerns the cryo-EM structure of the PRE-EF-G complexes obtained in the presence of the antibiotic spectinomycin (Spc) (112). In this structure, EF-G was initially reported to be in complex with GTP, which is surprising because GTP hydrolysis is very rapid [with the first round of GTP hydrolysis completed in less than 10 s (95), which is faster than the time needed for cryo-EM sample preparation] and is not inhibited by Spc (94). The mRNA–tRNA complex in the Spc-stalled translocation intermediate is partially unlocked (112), which is also surprising, as there is no unlocking in the PRE-EF-G–GDP–Pi structures that represent a later translocation intermediate (15, 95). Notably, the observed partial disruptions of the A-site mRNA–tRNA interactions in the Spc-stalled complex (112) may arise from the antibiotic-induced destabilization of A-site tRNA binding (94). Spc is known to affect the dynamics of the SSU head swiveling (7, 11), as well as the backward rotation of the SSU body (7). The alterations in ribosome dynamics by Spc shift the ribosome to slow gear (7, 31), as is also seen with nonhydrolyzable GTP analogs (6). Given the known effects of Spc, it is possible that the state observed in Reference 112 represents a very early GDP–Pi intermediate (15, 95) or is not an authentic translocation intermediate (95); further time-resolved cryo-EM structures of translocation in the absence of antibiotic will resolve this problem. Another open question is the mechanism of translocation in eukaryotes (4, 38, 63), where several mechanisms have been proposed that differ from that in the well-studied bacterial system. While the details of translocation may differ between prokaryotes and eukaryotes, the fundamental driving forces are likely to be the same; thus, more detailed biochemical, biophysical, and structural studies of the mechanism in the mammalian system are necessary.

Reading Frame Maintenance and Spontaneous Frameshifting

For most codon combinations, the two tRNAs that move from the A to P and from the P to E sites of the ribosome remain bound to their respective codons because codon–anticodon base pairing in the -1 or $+1$ frame is thermodynamically unfavorable due to mismatches. This is, however, different for mRNA sequences of the type X XXY YYZ, which are called slippery sequences. Often, the same tRNA can read both the 0-frame XXY and the -1 -frame XXX due to wobble base pairing at the third codon position. In such cases, tRNA can unbind from the codon and rebound to its thermodynamically favored codon in a wrong reading frame (10); for example, assuming the same affinity of a tRNA for the XXX and XXY codons, 50% of ribosomes are expected to shift to the -1 frame if given enough time. However, this normally does not occur, which raises the question of how translating ribosomes maintain the reading frame on slippery sequences.

In the PRE state, the codon–anticodon complex in the A site is stabilized by interactions with G530, A1492, and A1493 in 16S rRNA of the SSU (88). These interactions have to be resolved at some point in translocation to allow the tRNAs to move, and structural studies on the mechanism of translocation show that this resolution occurs in the CHI state. As the tRNA–mRNA complex moves out of the A site on the SSU body domain, the interaction with the universally conserved bases of 16S rRNA is disrupted (143). In the absence of EF-G, the tRNA tends to move toward the -1 -frame codon, which would favor frameshifting. In the presence of EF-G, D4 stabilizes the codon–anticodon duplex due to interactions of the conserved His583 and Gln507 of EF-G with the backbone of the A-site tRNA (15, 95, 112, 142). Mutating these residues increases the spontaneous -1 -slippage dramatically (85, 93) (**Figure 4**). Notably, there is a clear correlation between the rate of translocation and frameshifting, which was used to estimate the lower limit for the rate of spontaneous frameshifting, approximately $1\text{--}10\text{ s}^{-1}$ (93). Recent smFRET experiments provide an even more detailed picture (96). On a slippery sequence, some ribosomes in the population switch from rapid, accurate translation to a slow mode in which the movements of the tRNAs in the A and P sites are uncoupled. Peptidyl-tRNA rapidly moves to the CHI state but does not complete translocation and instead continues sampling the CHI and POST (A/A) states, which also hinders closing of the SSU head domain. At the same time, the P-site tRNA moves through the E site and dissociates from the ribosome. This opens a time window for the peptidyl-tRNA to select the favorable -1 -frame unhindered by the deacylated tRNA interactions with the preceding codon (96). These data demonstrate the importance of the coupled movements of tRNAs and EF-G for rapid and accurate translocation.

Interestingly, ribosome switching to a slow gear seems to be a general strategy to deal with obstacles during translocation. Force measurements suggest that ribosomes switch from the fast to the slow gear to unwind mRNA hairpins (24). However, there is a marked difference between the resulting slow gears induced by an mRNA hairpin and a slippery sequence (96). Unwinding of the hairpin slows down a very early step of translocation upon which the SSU head domain rotates forward prior to tRNA movement into the CHI state (24). Ribosomes proceed in reversible subcodon steps against the obstacle, suggesting that they exploit fluctuations on the mRNA to overcome the mechanical barrier (24, 97). In contrast, frameshifting is induced at the late steps of translocation, when the tRNA moves between the CHI and POST states and the SSU head domain moves backward; notably, slowing down the steps before CHI formation does not result in frameshifting (96). Thus, while switching gears seems to be a general ribosome response, the timing of the slow step defines the translational outcome.

RECODING

Recoding defines cases in which decoding rules are altered through the action of specific signals in the mRNA sequences (44). Recoding differs from the genetic code redefinition, which changes the

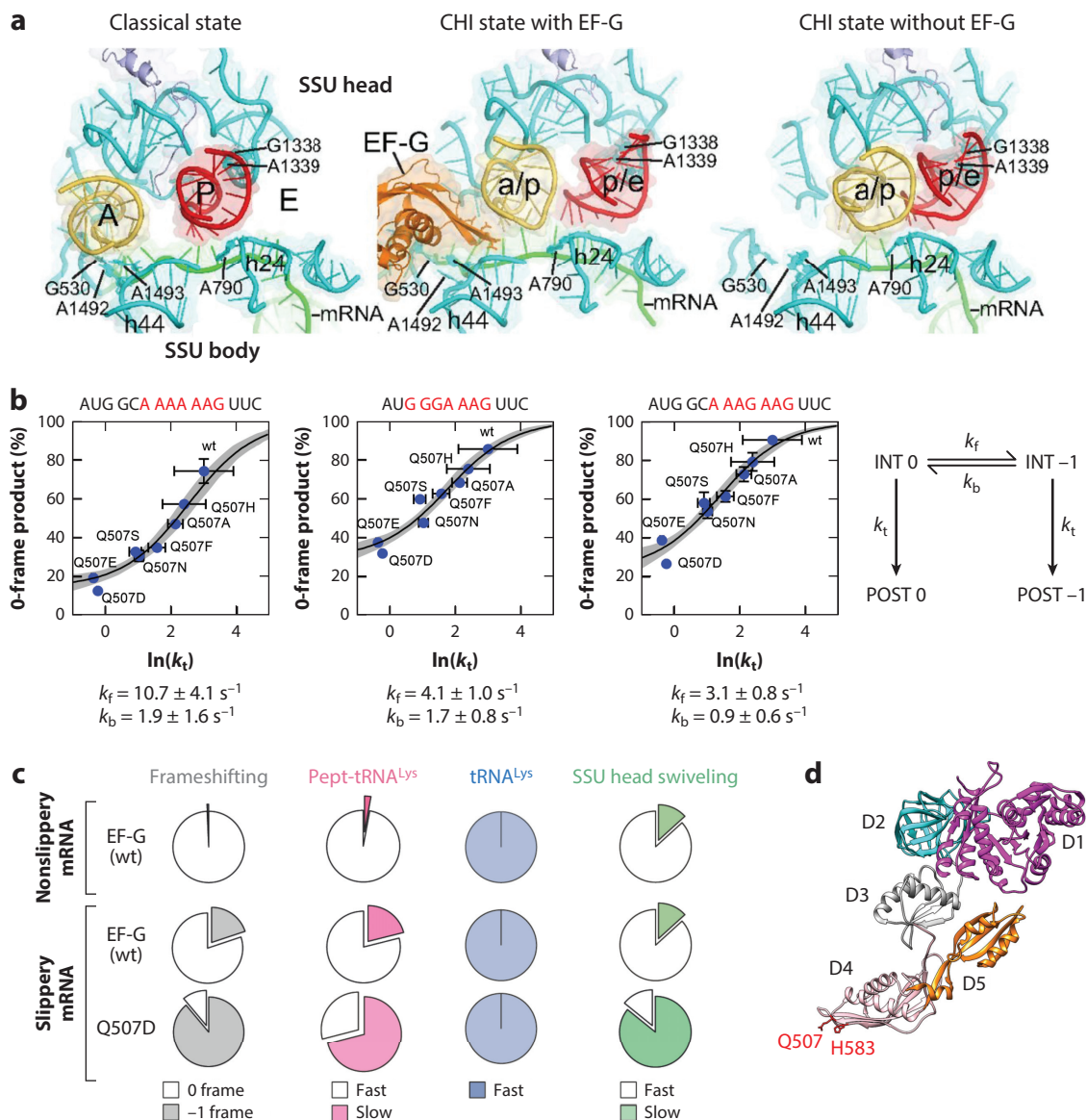


Figure 4

Reading frame maintenance. (a) Contacts of the A-site tRNA anticodon in the ground classical state and in the translocation intermediate CHI state with and without EF-G (142, 143). Shown are tRNA anticodons in the A and P sites. The extensive interaction in the C state between the codon-anticodon complex and 16S rRNA residues A1492, A1493, and G530 in the SSU body domain is disrupted upon displacement of the tRNAs into the CHI state. EF-G interacts with the tRNA and the SSU head and keeps the tRNA in place. In the absence of EF-G, the ap/P-tRNA anticodon tends to move out of the reading frame register. Panel reproduced from Reference 143. (b) Mutations of EF-G residues Q507 and H583 at the tip of D4 slow down translocation (k_t) and induce -1 -frameshifting, resulting in the decrease of the fraction of the 0-frame product. Continuous lines show fits of the data to a model (right) where the tRNAs can slip from the 0- to -1 -frame while delayed in the CHI state and before translocation is completed; this model provides estimates for the transitions to and from the -1 -frame in the CHI state (93, 127). Panel reproduced from Reference 93. (c) Populations of fast, accurate and slow, frameshifting ribosomes calculated by an smFRET approach (96). (d) Positions of Q507 and H583 at the tip of EF-G D4. Abbreviations: CHI, chimeric; EF-G, elongation factor G; rRNA, ribosomal RNA; SSU, small ribosomal subunit; tRNA, transfer RNA.

codon meaning on the whole-genome scale, as in natural codon reassignment in mitochondrial genomes or engineered stop codon reassignment to a new synthetic aa-tRNA (22). In contrast, recoding does not alter genetic rules for the majority of genes and operates only on a fraction of the genome. Recoding can occur in the A site, for example when a stop codon is read by an aa-tRNA, resulting in a translational readthrough (TR). Frameshifting is another prevalent recoding event. Spontaneous ribosome frameshifting and programmed ribosome frameshifting (PRF) occur during translocation, except for in cases when frameshifting is induced by the absence of a aa-tRNA reading the A-site codon of the slippery codon, which can lead to frameshifting of a single tRNA in the P site. In some cases the ribosome can skip a part of the mRNA and synthesize a single protein from a discontinuous reading frame, a phenomenon called translational bypassing (for reviews, see 101, 103). A common theme of frameshifting and bypassing events is the altered kinetics of translation at the point of recoding. However, it remains unclear whether this is also true for other types of recoding, such as TR.

Translational Readthrough

Sporadic misreading of a stop codon (UGA, UAG, or UAA) by aa-tRNA is very infrequent and is estimated to occur approximately 10^{-5} times per codon. However, programmed TR is more prevalent than was previously thought, and studies over the last decade have revealed the occurrence of TR in several eukaryotic systems (28, 59, 71, 83). Viruses use TR to expand the coding potential of their genomes in a way similar to how they use programmed ribosome frameshifting (35, 36, 54, 92). TR cases are found in mammalian, yeast, and mosquito cells (28, 32, 58, 83, 135). Computational analysis of protein isoforms produced by TR indicates that the extensions are mostly intrinsically disordered peptides of low sequence complexity. These C termini may help to alter the protein function without distorting the native protein core, for example, by changing the localization, stability, and function of the canonical isoform.

The TR efficiency depends on several factors, including the context of the stop codon and the relative availability of translational termination factors and aa-tRNAs that can misread stop codons. TR is most efficient on the UGA stop codon followed by a C (21, 55, 71, 77). Nucleotides +4 to +9 modulate TR in several viral and eukaryotic genes (5, 21, 50, 71, 128). Recent studies on the *Drosophila* TR candidate gene *traffic jam* (*tj*), which encodes a large Maf transcription factor, have shown that the expression of the longer TR isoform of Tj is tissue specific and translationally controlled. The expression of the Tj-TR isoform is important for the cells of the nervous system but is detrimental for gonad development. The high TR efficiency correlates with the tissue-specific expression of eRF1H, a splice variant of eukaryotic release factor eRF1 that appears to favor TR in leaky stop codon contexts. Strict control of TR on a transcription factor gene provides an important link between transcription and translation, which may be particularly relevant for nerve cells, which are under pressure to rapidly adapt to external stimuli and conditions. There is a growing list of mammalian genes that are known to undergo TR (for a review, see 75), although the functional relevance and the control mechanisms remain poorly understood. Eukaryotes employ several strategies to enlarge the coding capacity of their genomes, such as alternative splicing, alternative polyadenylation, frameshifting, and alternative initiation of translation (61, 65, 124, 126). TR is yet another strategy to increase the diversity of the proteome by supplying C-terminally extended protein isoforms with potentially altered physiological functions.

One special case of programmed TR is the recoding of stop codons by unconventional (but natural) amino acids, such as selenocysteine or pyrrolysine. Incorporation of selenocysteine at a dedicated UGA codon requires a specialized machinery and is modulated by mRNA secondary structures (for a review, see 103; for structures of bacterial and eukaryotic selenosomes, see 37, 51).

In contrast, pyrrolysine is incorporated at UAG codons, which are underused in those organisms—mostly methanogenic archaea—that encode tRNA^{Pyl} and the dedicated aa-tRNA synthetase.

–1 Programmed Ribosome Frameshifting

–1PRF is prevalent in viruses, including many human pathogens such as HIV-1, SARS, MERS, and CoV2. It is usually assumed that frameshifting ensures a specific constant ratio of the in- and out-of-frame products. However, recent results suggest that the frameshifting efficiency—and thus the ratio between the two gene products—can change with time (19), indicating an as-yet-unknown mechanism of temporal regulation. Frameshifting is also found in bacteria, for example, in the *dnaX* gene, which is the best-studied example of –1PRF (14, 17, 62, 138). A recently discovered case of –1PRF in bacteria is *copA*, where translation of the entire gene generates a membrane copper transporter, CopA, while –1PRF leads to premature termination and synthesis of the copper chaperone CopA(Z); similar frameshifting elements are found in the human homolog of CopA, *ATP7B* (79). In eukaryotes, frameshifting on canonical genes may constitute as much as 10% of the proteome (8, 111). Increased frameshifting due to defects in, e.g., tRNA modification or ribosome assembly and function leads to human diseases (25, 90, 105). However, to date, the only example of –1PRF in eukaryotes is Edr (Peg10), a protein important in embryonic development (76). The existence of –1PRF in CCR5, the HIV-1 coreceptor (9), could not be confirmed in subsequent experiments (60). In view of these recent negative results (60), the general notion that frameshifting in eukaryotic cells may contribute to the regulation of gene expression by affecting mRNA stability and decay (2) should be treated with appropriate caution.

The elements in the mRNA that promote –1PRF are the slippery sequence and an mRNA secondary structure element placed at a defined distance downstream of the slippery site. In the case of bacterial *dnaX* and a few other genes, there is a Shine-Dalgarno-like sequence upstream of the slippery sequence that contributes to high frameshifting efficiency. In some cases, trans-acting elements modulate frameshifting. Proteins can act as trans-regulators, as in the case of the porcine reproductive and respiratory syndrome virus (PRRSV) (19) or in Theiler's murine encephalomyelitis virus (TMEV) (52). In addition, G-quadruplexes (29, 139), microRNAs (9), or tRNA abundance in a particular cell type (66) can modulate –1PRF efficiency. For example, the exact frameshifting route and efficiency on the *gag-pol* site of HIV-1 depend on the accessibility of a rare tRNA^{Leu5} that reads the UUA codon at the frameshifting site. As the concentration of tRNA^{Leu5} varies by more than 20 times between different cell types, the ratio of the Gag and Pol viral proteins produced by –1PRF, and thus the efficiency of virus propagation, can vary from cell to cell (66). A similar tRNA-dependent modulation of frameshifting was also reported within the expanded CAG stretch in the *huntingtin* gene: The translation of expanded CAG repeats in mutant huntingtin exon 1 leads to a depletion of charged Gln-tRNA^{Gln}_{CUG} that pairs to the CAG codon, which results in translational frameshifting (45).

Mechanistic studies by kinetics and single-molecule methods have identified two major routes for –1PRF (**Figure 5**). In the major pathway identified for bacterial *dnaX*, HIV-1 *gag-pol*, avian infectious bronchitis virus (IBV) *1a/1b*, and Semliki Forest virus (SFV) *6K* mRNAs, frameshifting occurs during translocation of the two tRNAs bound to the slippery codons (13, 14, 17, 62, 67, 138). As with the spontaneous frameshifting, slippage occurs when the ribosome slows down while in the CHI state (13), but the fraction of frameshifting ribosomes is increased by the presence of a downstream mRNA structural element. In contrast to spontaneous frameshifting, where peptidyl-tRNA changes frame after the release of deacylated tRNA, two tRNAs slip during –1PRF. In both spontaneous and programmed frameshifting, closing of the SSU head domain is the step limiting further progression along the mRNA. In –1PRF, this may be resolved by moving the base of the

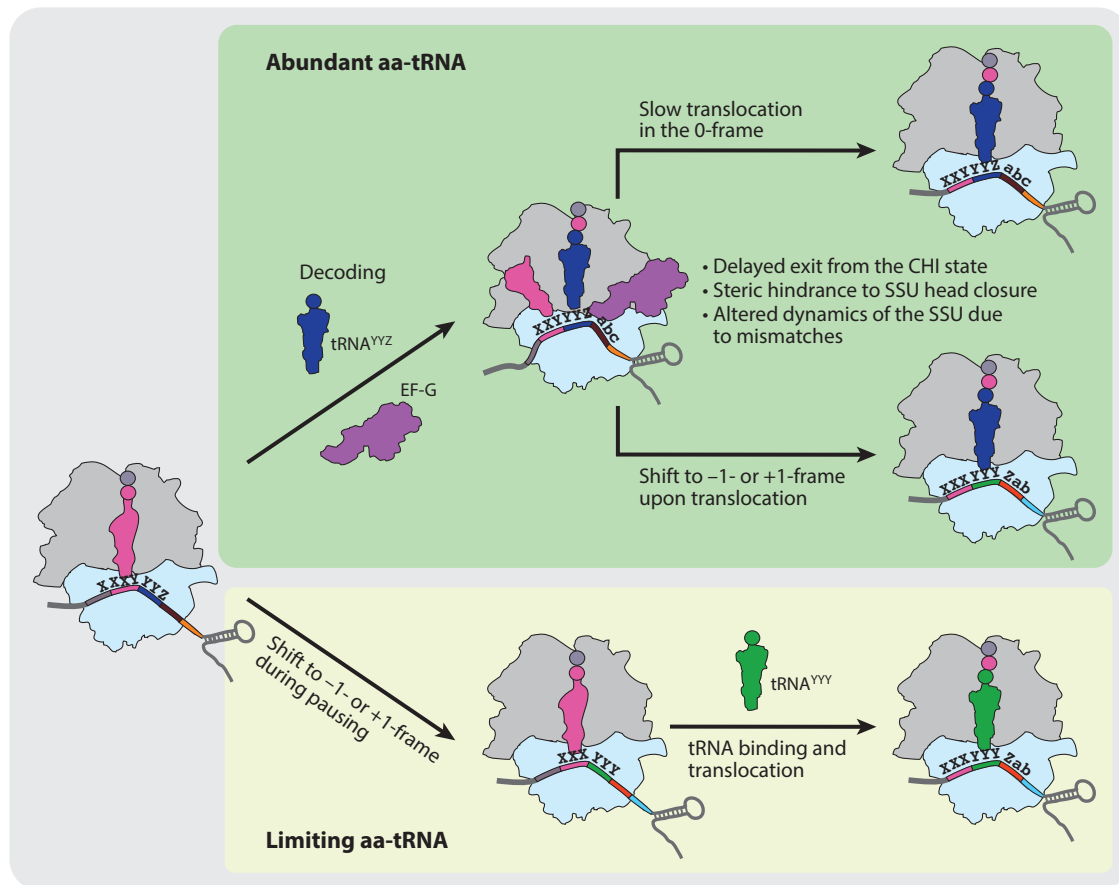


Figure 5

Frameshifting routes. (*Top*) Under conditions where aa-tRNA decoding of the slippery codon in the A site is abundant, translocation rapidly proceeds until the CHI state. Translocation obstacles, such as downstream mRNA structures (13) or altered SSU domain closure (23), block further progression along the translocation trajectory. With time, ribosome stalling is resolved by canonical translocation or by frameshifting to an alternative reading frame. (*Bottom*) Under aa-tRNA limitation, P-site tRNA can slip into the -1 frame (14), or an abundant aa-tRNA can bind in the +1 frame (41, 53). Abbreviations: aa-tRNA, aminoacyl tRNA; CHI, chimeric; mRNA, messenger RNA; SSU, small ribosomal subunit; tRNA, transfer RNA.

secondary structure element closer to the ribosome helicase center, which may help to unwind the mRNA and allow the ribosome to move forward (13).

An alternative route for -1PRF operates when a peptidyl-tRNA on a slippery codon resides in the P site and -aa-tRNA cognate to the A-site codon is not available (14, 17). Ribosome pausing to the hungry A site provides the time window for the P-site peptidyl-tRNA to slip into a thermodynamically favorable reading frame. In the case of -1PRF, frameshifting efficiency does not depend on the downstream secondary structure (14). Interestingly, this route of frameshifting becomes prevalent in tumors upon tryptophan deprivation (3). The resulting aberrant trans-frame peptides play a role in the immune recognition of melanoma cells by contributing to the diversification of the peptidome landscape. While Champagne et al. (16) also implied a role of ribosome collisions and ribosome quality control (RQC) system as a potential inducer of such frameshifting events, it is important to note that hungry frameshifting is elicited in vitro by starvation at

controlled conditions without ribosome stalling or any auxiliary RQC components. A direct role of RQC in frameshifting is also unlikely because it would facilitate degradation (rather than the observed accumulation) of the aberrant translation products. However, removal of the RQC components could have an indirect effect on the accumulation of the aberrant peptides by generating stress signals that suppress tumor progression (16, 137).

Mechanisms of +1 Frameshifting

Recent work on +1 frameshifting suggests that it also can occur through different routes. Similar to -1PRF, +1 frameshifting occurs on slippery mRNA sequences when ribosomes pause at the frameshift site. The ribosome pause can occur because of a limiting supply of a cognate aa-tRNA (120), nucleotide insertions at the anticodon loop of the tRNA (40, 41), or lack of tRNA post-transcriptional modifications (53, 129). In some cases, downstream mRNA elements modulate the +1 frameshifting efficiency, although how these interactions stimulate frameshifting remains unclear (49, 56, 123). One of the best-studied cases is +1 frameshifting on the mRNA sequences CC[C/U]-N, which is decoded by tRNA^{P_{ro}} (23, 41). Kinetics studies using SufB2, a +1 frameshifting-prone tRNA^{P_{ro}} (GGG) mutant, which contains an insertion after nucleotide 37 (G37a) in the anticodon loop, suggest two potential frameshifting routes (41). The major route takes place during EF-G-catalyzed translocation of the tRNA from the 0-frame position in the A site to the +1-frame position in the P site. The additional route operates through an unconventional shift within the P site upon occupancy of the A site in the +1-frame position (41). Cryo-EM and crystal structures suggest that, during decoding, tRNA^{P_{he}} maintains its 0-frame anticodon-codon pairing even if there is an unfavorable wobble cmo⁵U34-C3 base pair formed between the tRNA^{P_{ro}}(UGG) and the codon CCC or a nucleotide insertion in the tRNA anticodon (23, 33). Interestingly, unlike the 0-frame complexes containing the cmo⁵U34-A3 base pair, the structure of the complex with cmo⁵U34-C3 shows an open SSU conformation, which possibly destabilizes the labile codon-anticodon helix containing the cmo⁵U34-C3 pair (23). Limited space in the A site seems to restrict the codon-anticodon dynamics and thereby prevents slippage in this pretranslocation state. However, upon translocation, the ribosome switches to the +1-frame in the CHI state (23). The complex remains frameshifted until the completion of translocation of tRNA^{P_{ro}} to the P site. This work suggests that noncanonical pairing in the pretranslocation complex sets the stage for frameshifting by opening the SSU and promoting frameshifting during EF-G-catalyzed translocation (23). In addition, crystal structures of tRNA^{P_{ro}} lacking the chemical modification at m¹G37 suggest that the lack of the modification destabilizes interactions of tRNA^{P_{ro}} with the P site of the ribosome, causing a conformational rearrangement typically only seen during EF-G-mediated translocation (53). Together, these findings suggest that the fundamental mechanisms of -1 and +1 frameshifting may be similar and that slow translocation may be a predominant route regardless of the frameshift direction (Figure 5).

PERSPECTIVES

Recoding is a remarkable way to alter gene expression programs depending on the status of the cell. Studies of translational readthrough show how expression of an alternative isoform of a termination factor ensures expression of a longer protein isoform in a specific tissue. Frameshifting is regulated by the availability of particular tRNAs, which in eukaryotes is cell and tissue specific. Recent studies suggested that ribosome pausing is a hallmark of recoding events and elucidated mechanisms of frameshifting and translational bypassing. One factor that remains elusive is the dynamics of downstream mRNA elements that modulate frameshifting. Future structural work will show which interactions induce ribosome pausing and how pausing is alleviated by frameshifting.

The most important challenge in this work is to elucidate the mechanisms of translation in eukaryotes in enough depth to allow us to understand the dynamics of translational components. This remains challenging due to the limited availability of fully reconstituted mammalian translation systems and difficulties in introducing reporters (such as fluorescence labels) into the translational components. Ribosome profiling, mass spectrometry, and cryo-EM methods provide a wealth of information, which in the future will be combined with biophysical techniques to provide insights into gene expression programs in higher eukaryotes.

Another unresolved issue is the effect of decoding errors on cellular fitness and evolution. While the majority of errors are likely detrimental, the ability to produce altered proteins may enable cell survival during periods of stress. It will be important to clarify which errors are particularly deleterious and how cellular chaperones and proteases adapt to different levels of translation errors. Potential effects of codon context and codon position in the mRNA sequence on translational fidelity is an important area of future research. One exciting avenue is to understand how tRNA abundance and chemical modifications affect translational fidelity and how this changes cell fitness. This is particularly interesting in view of differential tRNA expression in different tissues and its potential link to human diseases. Unraveling the prevalence, mechanisms, and functional roles of TR, in particular in mammals, will contribute to our understanding of the regulatory links governing cell-type-specific expression programs. Decoding and recoding are important in human diseases, such as cancer, and it will be essential to identify how translation changes during development, aging, and diseases. Understanding the mechanisms governing translation fidelity and regulating the response to environmental cues is essential to developing new approaches for medicine and biotechnology.

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The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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