Translational Frameshifts Induced by Mutant Species of the Polypeptide Chain Elongation Factor Tu of Escherichia coli*

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Translational frameshifts, both +1 and -1, are promoted by mutations in\textit{tuFA} and \textit{tuFB}, the two genes encoding the polypeptide chain elongation factor (EF) Tu of \textit{Escherichia coli}. Strains harboring the mutant EF-Tu(Ala$^{278}$-Thr) encoded by either \textit{tuFA} or \textit{tuFB} or by both, display a linear relationship between the frequency of frameshifting and the concentration of mutant EF-Tu, relative to the total amount of EF-Tu. A second mutant species, EF-TuB(Gly$^{222}$-Asp), also promotes frameshifting. The frequency is strikingly enhanced by the combined action of EF-TuA(Ala$^{278}$-Thr) and EF-TuB(Gly$^{222}$-Asp) and exceeds by far the total contribution of the two mutant EF-Tu studied separately. These observations raise the question whether the formation of each peptide bond under conditions that no frameshifting occurs also requires the combined action of two EF-Tu molecules, in this case not differing functionally.

The mechanism underlying the maintenance of the translational reading frame during polypeptide chain elongation is poorly understood. Although various members of the translational machinery are known to participate in each elongation step, their contribution, if any, to the correct readout of the three base-encoded messages has not always been assessed in detail. The role of two main interaction partners in this process, tRNA and mRNA, is illustrated by various features causing frameshifts such as "tRNA hops," "hungry codons," "shifty stops," and "shifty Shine and Dalgarno-like sequences" (Weiss et al., 1988, a and b; Spanjaard and van Duin, 1988; Falahee et al., 1988; Weiss et al., 1987; Weiss and Gallant, 1983). Since a shift of the reading frame in general is abortive for translation, it is conceivable that the cell has much to invest in avoiding such an event (Kurland and Ehrenberg, 1985). Interestingly, the translation apparatus occasionally turns such an event to its own advantage and employs frameshifting to complete and regulate the synthesis of a correct protein. Telling examples are the synthesis of each peptide bond under conditions that no frameshifting occurs also requires the combined action of two EF-Tu molecules, in this case not differing functionally.

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**MATERIALS AND METHODS

\textbf{Strains}—The \textit{E. coli} K12 strains used in this study are listed in Table 1. All strains are isogenic except for the \textit{tuA} and \textit{tuB} mutations and the markers used for strain constructions, \textit{repB} and \textit{fus}. Strains EV104, EV105, and EV114 were constructed with \textit{P}$_1$ transduction (Miller, 1972). The donor strain, KMBL1164 (supE, thi, \textit{Δpro-lac}), was used to transduce the \textit{Δpro-lac} region to EV100, EV102, and EV110 (Vijgenboom and Bosch, 1987), respectively.

\textbf{Plasmids}—Frameshift mutations are indicated according to the convention established by Crick and Brenner (1967) and expounded in Weiss et al. (1988a).

The plasmids pWS60 and pWS50 are generously provided by Dr. D. Court. All plasmids described in this paper are derivatives of pWS60 on which the gene for Cas is fused with a \textit{BamH}I linker to the coding sequence of \textit{lacZ}. The gene fusion is under the control of the \textit{λ-P}$_\textit{r}$ promoter. The fusion protein consists of the first 12 amino acids of Cas and all the amino acids of \textit{β}-galactosidase except for the eight N-terminal amino acids. The plasmid pWS50 does not produce the fusion product due to an insertion of 20 bases in the Cas part of the fusion which results in a -1 frameshift mutation. The plasmids pWS60.1 and pWS60.7 were constructed by, respectively, filling and deleting the sticky ends of the \textit{BamH}I site at the fusion point.
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TABLE I

| Strain | Genotype          | Reference                  |
|--------|-------------------|----------------------------|
| EV2    | Δ(pro-lac)        | Vijgenboom et al., 1985    |
| EV3    | tuBΔ BΔ proB Δ(pro-lac) | Vijgenboom et al., 1985    |
| Ev4    | tuBΔ proB Δ(pro-lac) | Vijgenboom et al., 1985    |
| EV5    | tuBΔ proB Δ(pro-lac) | Vijgenboom et al., 1985    |
| EV8    | tuAΔ fus Δ(pro-lac) | This paper                 |
| EV9    | tuAΔ tuBΔ proB fus Δ(pro-lac) | This paper                 |
| EV104  | tuAΔ fus Δ(pro-lac) | This paper                 |
| EV105  | tuBΔ proB fus Δ(pro-lac) | This paper                 |
| EV113  | tuAΔ tuBΔ proB fus Δ(pro-lac) | Vigenboom and Bosch, 1987 |
| EV114  | tuAΔ tuBΔ proB fus Δ(pro-lac) | Vigenboom and Bosch, 1987 |

* Coding for EF-TuB (Gly272→Asp).
* Coding for EF-TuA (Ala275→Thr).
* Coding for EF-TuB (Ala275→Thr).
* Coding for EF-TuA.

**Results**

Error-prone Mutant EF-Tus—The frequency of ribosomal frameshifting, induced by mutant species of EF-Tu, was determined in E. coli strains (Table II) transformed with plasmids harboring a frameshift mutation in a CII-lacZ fusion (see Fig. 1 and "Materials and Methods"). Full length fusion products with β-galactosidase activity are formed upon ribosomal reading of the fusion construct. The presence of the frameshifting, induced by mutant species of EF-Tu, was determined by rocket immunoelectrophoresis with antibodies raised against EF-Tu (van der Meide et al., 1982).

**Table II**

| Strain | Frameshift construct |
|--------|----------------------|
|        | pWS60Δ (wild type)   |
|        | pWS60β                 |
|        | pWS60α (+1)           |
|        | pWS60α (+1)           |
|        | pWS60.1 (−1)          |
|        | pWS60.3 (+1)          |
|        | pWS60.5 (−1)          |
|        | (% )                  |
|        | %                    |
| EV2 (AB) | 100 0.02 0.005 0.01 0.001 0.005 |

* The β-galactosidase activity is expressed as the percentage of the wild type construct, pWS60α.

The capital letters in parentheses indicate the EF-Tus. Wild type = A and B. Mutation at amino acid position 376, Ala-Thr = A, and B. Mutation at amino acid position 222, Gly→Asp = B. Mutation at unknown position = A*.

**Fig. 1. Frameshift mutations in pWS60.** The wild type sequence of the fusion CII-lacZ is drawn in the middle of the figure. Derivatives harboring a frameshift mutation in the CII part of the fusion are in the lower part of the figure, and those with a frameshift mutation in the lacZ part of the fusion in the upper part. Insertions, due to the construction of the frameshift mutation, are underlined, and relevant restriction sites are double underlined. The codon for the first amino acid in the correct frame 3' of the frameshift mutation is indicated with the corresponding amino acid number and a line above the sequence. The numbering is relative to the start codon (0) for the frameshift mutations in the CII part (No. 16 = No. 9 of the wild type lacZ sequence) and according to lacZ for the mutations in pWS60α and pWS60β. These amino acids indicated with a prime are the first amino acids changed due to the frameshift mutation.
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| Strain* | Frameshift constructs* |
|---------|-----------------------|
|         | pWS50 (-1) | pWS60.7 (+1) | pWS601.3 (+1) | pWS60.5 (-1) | pWS60.1 (+1) |
| EV2 (AB)* | 1 | 1 | 1 | 1 | 1 |
| EV5 (AB), | 12 | 77 | 43 | 13 | 27 |
| EV6 (AB), | 1 | 3 | 2 | 1 | 2 |
| EV3 (AB), | 1 | 3 | 3 | 2 | 2 |
| EV4 (A) | 1 | 2 | 1 | 2 | 1 |
| EV9 (A) | 1 | 4 | 5 | ND | ND |
| EV114 (A*B) | 8 | 24 | 36 | ND | ND |
| EV113 (A*) | 2 | 2 | 1 | ND | ND |

* See Footnote b, Table II.

The β-galactosidase activity is normalized to the wild type strain EV2, transformed with the same frameshift construct.

ND, not determined.

online, and EF-TuA* has an unknown amino acid substitution. One of the two mutant EF-TuB species (EF-TuB,) has aspartic acid substituted for glycine-222, the other (EF-TuB,) is identical with EF-TuB, (except for the difference in C terminus also found in wild type EF-TuA and EF-TuB). In some strains, tuB has been inactivated by insertion of the bacteriophage Mu (compare Table I).

As is apparent from Table III, the level of frameshifting is raised maximally in strains carrying mutations in both tuf genes: EV(A,B) and EV114(A*B). Strains with a mutant and a wild type EF-Tu such as EV8(A,B) and EV3(A,B), display levels of frameshifting only slightly higher than that of the wild type strain. That EF-TuA is error-prone, indeed, is shown more significantly by inactivation of the wild type tuB gene. The β-galactosidase of strain EV9(A) is approximately 2 to 5 times higher than that of strain EV4(A). EF-TuA* of strain EV113(A*) also promotes frameshifting above the background level of strain EV4(A). The contribution of EF-TuB, to frameshifting cannot be studied separately, since inactivation of tuA is lethal to the cell and the procedure successfully applied to transfer the mutation, Ala375+Thr to tuB or tuF (Vijgenboom and Bosch, 1987), failed in transferring the mutation Gly222→Asp to the chromosomal tuA.

A notable finding presented in Table III is that the frameshift levels caused by the single tuF gene mutations of the strains EV8(A,B) and EV3(A,B) are not additive in the double mutant EV5(A,B). The same, most likely, is true for the frameshifts measured in the strain EV114(A*B), although the combination of this mutant tuF with wild type tuB has not been studied. This synergism between the mutant species of EF-TuA and EF-TuB raises interesting mechanistic questions (see "Discussion"). It is also noteworthy that combinations of EF-TuB, with EF-TuA, or with EF-TuA* suppress both +1 and -1 frameshift mutations. Preference for suppression of +1 frameshifts is suggested by the data obtained with frameshift mutations in the C, portion of the C4-lacZ fusion. The data may be biased, however, by the different codon contexts of the mutations. An indication for the effect of codon context may be derived from the differences in suppression of +1 frameshift mutations at position 14 of the C, lacZ fusion.

Frameshifting Is Dependent on the Mutant EF-Tu Concentration — The extent of frameshifting, induced by the error-prone A, mutation of tuA, is decreased when the cell harbors in addition a wild type tuB, as can be concluded from the β-galactosidase activities of strains EV8(A,B) and EV9(A).

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ternary complexes with the ribosome (Millar et al., 1978) or in their ability to sustain protein synthesis.3

A striking exception to the strains displaying the frameshifting pattern shown in Table IV and Fig. 2 is the strain EV5(A,B),. As shown in Table III, frameshifting in this strain exceeds by far that in all other strains studied here. Raising the EF-TuA concentration of this strain by transformation with pA, lowers the level of frameshifting (Table IV) in contrast to the increased frameshifting seen upon raising the EF-TuA, concentration of cells lacking EF-TuB,. The consequence of the raised EF-TuA(Ala77→Thr) concentration is a reduction in the relative concentration EF-TuB, participating in protein synthesis. As a result, frameshifting drops to the level of pA, transformants of the EV104(A,B) strain since the synergistic effect of the combination: EF-Tu(Gly222→Asp)/EF-Tu(Ala77→Thr) is now strongly reduced (compare the last four lines of Table IV).

DISCUSSION

Shifted EF-Tu—The results of the present paper show that mutant species of EF-Tu from E. coli induce frameshifting at moderate frequencies. A similar phenomenon has been reported by Hughes et al. (1987) for mutant EF-Tu from S. typhimurium and by Sandbaker and Ciubertson (1980) for mutant EF-1α. These findings suggest that wild type EF-Tu plays an important role in the maintenance of the correct reading frame during translation of the mRNA. Since mutant EF-Tu* also promote ribosomal readthrough of nonsense codons (Vijgenboom et al., 1985; Hughes, 1987; Hughes et al., 1987) and missense errors (Tapio and Kurland, 1986), a more general function of EF-Tu in regulating translational accuracy may be assumed.

EF-TuA(Ala77→Thr), competent in sustaining in vivo polypeptide synthesis, is error-prone. This can be concluded from the frequency of frameshifting in a strain producing EF-TuA, as the sole EF-Tu species (strain EV9(A), Table III). Previously, we did not find readthrough of stop codons to be increased in this strain (Vijgenboom et al., 1985). Studying the same mutant EF-Tu* in vitro, Tapio and Kurland (1986) measured an increased missense error.

Elevation of EF-TuA(Ala77→Thr) in E. coli cells (either EF-TuA, or EF-TuB, or both) revealed a linear relationship between the frequency of frameshifting and the concentration of mutant EF-Tu relative to the total EF-Tu population (Fig. 2). No plateau level of frameshifting was observed, even at relative mutant EF-Tu concentrations up to 220% (in pA, transformants of EV104(A,B); see Table IV). This may be ascribed to the lowered affinity of the mutant EF-Tu to GTP for aminoacyl-tRNA (Sain, 1983; van der Meide et al., 1983; Tapio and Kurland, 1989), although the relatively small difference in binding constants measured in vitro may not fully account for the data measured in vivo. The conclusion from Fig. 2 is that the frequency of frameshifting depends on the concentration of ternary complexes containing EF-TuA(Ala77→Thr) in the cell. In vitro studies of the function of these ternary complexes in protein synthesis (Düsterwinkel et al., 1981; van der Meide et al., 1981) or in vivo studies with cells producing EF-TuA, only (van der Meide et al., 1982, 1983) yield a ready explanation for the role of EF-TuA, in frameshifting. Suboptimal concentrations of ternary complexes and translational errors can explain the lower growth rates of strains EV9(A) and EV104(A,B), as compared to those of the wild type strains EV4(A) and EV2(AB) (data not shown).

The error-prone character of EF-TuB(Gly222→Asp) cannot be determined separately, since tufA cannot be inactivated, and attempts to isolate strains with EF-Tu(Gly222→Asp) as the sole tuf gene product failed (Vijgenboom and Bosch, 1987). Frameshifting was therefore studied in strains that harbor EF-TuB, in combination with mutant or wild type EF-TuA. EV3(AB), cells are not telling much since their frameshift frequency exceeds only slightly the background level. That of strains EV7(AB), and EV114(A,B),, however, clearly demonstrates the error-prone behavior of EF-TuB, since frameshifting at that level cannot be ascribed to EF-TuA, or EF-TuA* alone (Table III, Table IV, and Fig. 2). Again, as in the case of EF-TuA*, neither in vivo nor in vitro data regarding the participation of EF-TuB, in protein synthesis lend themselves to an interpretation of the functioning of EF-TuB, in frameshifting. In vitro translation experiments with poly(U) and purified EF-TuB, showed a reduced misincorporation of Leu at high Mg2+ concentrations as compared to that with wild type EF-Tu. Furthermore, in vitro experiments suggested a defective GTPase for EF-TuB, which was ascribed primarily to an anomalous interaction of the ternary complex with the ribosome (Swart et al., 1987). At low Mg2+ concentrations, EF-TuB, appeared to be unable to sustain poly(U)-directed polypeptide synthesis (Swart et al., 1987; Tapio and Kurland, 1986), but further in vitro translation experiments using natural messengers have to be awaited.

EF-TuA* has been poorly characterized, both structurally and functionally. It sustains weak frameshifting in vivo (Vijgenboom and Bosch, 1987), and we have to conclude from the results that this mutant EF-Tu is error-prone (compare strains EV113(A*) and EV114(A*B) in Table III).

Synergistic Action of Two Different Mutant EF-Tu Species—The synergistic effect on frameshifting exerted by the combinations EF-TuA/,EF-TuB, (EV5) and EF-TuA/*EF-TuB, (EV114) is striking. Since the frameshifting caused by EF-TuB, in cells, harboring this mutant species as the sole EF-Tu, cannot be determined, we cannot exclude that the low frequency observed with the EF-TuB/wild type EF-Tu(EV3) combination is due to an antagonistic action of the wild type species. If so, the synergism recorded in Table III is only apparent, and the high frequency observed with the double mutant combinations has to be ascribed to a high intrinsic frameshifting capacity of EF-TuB, exceeding by far that of EF-TuA,. In that case, wild type EF-Tu interacts with EF-TuB, thus reducing the extent of frameshifting. Alternatively, each of the mutant EF-Tus has a low intrinsic frameshifting capacity, but when co-existing in the cell, they exert a genuine synergistic effect. Also in that case one has to assume interactions of the two EF-Tus during the frameshift event. If frameshifting occurs within one single translational step, which is likely, this may have implications for the mechanism of translation under normal conditions when perturbation of the reading frame does not occur.

The frequency of frameshifting is strongly reduced by the introduction into EV5(AB), cells of plasmid-borne EF-TuA, in contrast to the increase in frameshifting observed upon introduction of EF-TuA, into cells lacking EF-TuB,. Due to the anomalous interaction of EF-TuB, with ribosomes (Swart et al., 1987), ternary complexes containing EF-TuA, may effectively compete with ternary complexes containing EF-TuB, for ribosomal binding sites. Raising the EF-TuA, concentration will then cause a relatively pronounced reduction in the participation of EF-TuB, in protein synthesis and thus in the synergism of the two mutant EF-Tu species. We also found synergism with EF-TuA, and EF-TuB, when studying nonsense readthrough in the same strains (Vijgenboom et al., 1985). Frameshift and nonsense suppression studies performed with EF-Tu mutants in S. typhimurium,
with unknown amino acid substitutions, did not reveal any synergism (Hughes et al., 1987). While confirming synergism in nonsense suppression by EF-TuA, and EF-TuB, in strain EV5, Tapio and Isakkson (1987) noticed that the synergism disappeared when studies were performed in a different genetic environment. We conclude that a synergistic effect, if any, of two different species of mutant EF-Tu in promoting translational errors may become apparent depending on the nature of the mutations and on the genetic constitution of the cell. The linear relationship between the relative concentration in the cell of EF-Tu (Ala)⁷₃ → Thr) and the frequency of frameshifting (Fig. 2) showing that no synergism becomes apparent under these conditions, may indicate that synergism requires the combined action of two different mutant EF-Tu molecules.

The Mechanism of Ribosomal Frameshifting—Several causes of ribosomal frameshifting have been reported in the literature. Frameshifts can be induced by Shine and Dalgarno-like sequences in the coding region of a gene (Weiss et al., 1988b). Pausing at codons that are translated by minor tRNAs or tRNAs that are temporarily at low concentration (Spanjaard and Van Duin, 1988; Weiss et al., 1988a) can result in a shift of the reading frame. Shifty stop codons or "ribosomal jumps" (Weiss et al., 1987) have been shown to be involved.

In order to see whether one or more of these mechanisms play a role in the phenomena presently described, the frameshift window for each of the five frameshift constructs has been depicted in Fig. 3. The constructs pWS60.1 and pWS60.5, carrying a +1 frameshift mutation in the CII part of the fusion, share the first 13 codons of their frameshift windows. The difference in frameshift suppression observed with these constructs, therefore, has to be related to the sequence downstream of these 13 codons. The nucleotide sequences overlapping codons 12 to 14 of both windows display complementarity to the nucleotide sequence 1535–1540 (5’CCUCCU 3’) near the 3’-end of 16 S rRNA:

That base-pairing, as depicted above, may lead to ribosomal frameshifting, has been demonstrated by Weiss et al. (1988b) for certain nucleotide stretches of the mRNA. Here, the effect of the interaction on frameshifting may be enhanced by the presence of mutant EF-Tu. Such a mechanism cannot explain the frameshifting observed with the constructs pWS50, pWS60.3, and pWS60.5, however, as an inspection of their window sequences shows.

In the constructs pWS60.3 and pWS60.5, the change of the reading frame has to occur close to the mutation site, located in the middle of the lacZ coding region, since preservation of the β-galactosidase activity does not permit extensive alterations of the primary structure. This restricts the number of possible frameshifts with these constructs and makes the combined action of a minor tRNA and mutant EF-Tu unlikely. Frameshift at a shifty stop codon is excluded in the case of pWS60.3 since the stop codon in the 0 frame is too far away from the frameshift mutation (130 base pairs) and thus would lead to loss of enzymic activity.

In conclusion, no common mechanism underlying frameshifting in all constructs studied here can be offered. The possibility of mutant EF-Tu, inducing shifts at random along the messenger chain, both to the +1 and −1 frame, may be envisaged leaving beside some preference for sites in certain codon contexts.

The recent finding (Moazed et al., 1988) that EF-Tu and EF-G both interact with a common region on the 23 S rRNA may indicate that mutant EF-Tu perturbs a proper translocation of the ribosome along the messenger, resulting in an alteration of the translational reading frame. Whatever the mechanism of such a perturbation is, it has to account for the present finding that the cooperation between two EF-Tu molecules can enhance the frameshifting disproportionately.
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This finding raises the question of whether such a cooperation is restricted to frameshift events in the mutated cell, or that each peptide bond formation in the wild type cell also requires the combined action of two EF-Tu molecules, which in the latter case are functionally identical. This possibility, forwarded earlier (Vijgenboom et al., 1985), may imply that the lack of a profound insight into the mechanism of polypeptide chain elongation forms one of the major obstacles to an understanding of the mechanism of frameshifting promoted by mutant species of EF-Tu.

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