RIBOSOMAL FRAMESHIFT AND FRAME-JUMP SITES AS CONTROL POINTS DURING ELONGATION

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Introduction

As the details of the interactions amongst tRNA, elongation factors, ribosomes and mRNA during the elongation phase of protein synthesis come into increasing focus, several new avenues for translational control have emerged. The recent advent of the high-level ribosomal frameshift site has opened up one such avenue for alternative events during the elongation and termination phases. These extreme cases of sequence-dependent variation in reading frame step size have also exposed a new lead into unsuspected interactions that occur during decoding and translocation. Analysis of ribosomal frameshifting is thus informative both from the standpoint of novel genetic control mechanisms, as well as illuminating new, and complex, macromolecular interactions occurring in protein synthesis.

At first glance, the capacity for altering the progress or reading frame of an elongating ribosome would not seem to unveil enormous vistas of genetic regulation. Indeed, the increasingly common recurrence of the retroviral gag-pol type -1 frameshift class in diverse eukaryotic and prokaryotic genes argues for a limited set of mechanisms and circumstances where efficient ribosomal frameshifting makes sense.

Currently, there are three examples of high-level ribosomal frameshifting where the site of the reading frame change has been pinpointed by protein sequencing. This article will briefly consider the 'how' of these various frameshifts before engaging in a more speculative treatment of the 'why'.

High-level ribosomal frameshift sites comprise multiple sequence features

Historically, translational frameshifting was studied from either a genetic approach, such as extragenic frameshift suppressors (a veritable plethora of alterations in both tRNAs, elongation factors and rRNA have been discovered by this approach; for a recent synopsis see O'Connor et al., 1989; and Culbertson, et al., 1989) or a physiological approach that investigated the relationship between aminoacyl-tRNA selection and reading frame maintenance (for an excellent review of all these subjects see Parker, 1989). Many of these studies emphasized the importance of interactions between the ribosome and ternary complex necessary for correct substrate selection, as well as the details of codon:anticodon interaction that gives the major definition to the ribosome's reading frame. What was not well understood in these early studies was the contribution of mRNA sequence to reading frame maintenance, although variation in the leakiness of some frameshift mutations presaged this topic (Fox and Weiss-Brummer, 1980; Atkins et al., 1983).

Appreciation of the mRNA's contribution to reading frame maintenance for the normal translation apparatus began to grow as the list of naturally-occurring high-level ribosomal frameshift events in certain genes began to expand (Dunn and Studier, 1983; Jacks and Varmus, 1985; Craigen et al., 1985; Clare and Farabaugh, 1985; Mellor et al., 1985; Moore et al., 1987, Brierly et al.; 1987, Huang et al., 1988; Clare et al., 1988; Sekine and Ohtsubo, 1989). This remarkable class of translational events range in rates from 5% to nearly 100% of ribosomes frameshifting at a specific sequence, and in altered step size of -1 or +1 nucleotides for the frameshift class, up to +50 nucleotides for the frame-jump class.

A unifying rule for the examples where the frameshift site has been localized by protein sequencing is the potential for stable anticodon pairing of the frameshifting tRNA (or tRNAs) with a codon outside the zero frame. Frameshifting on strings of repetitive nucleotides obey this rule, as seen with the +1 frameshift in the E. coli release factor 2 gene (Craigen et al.,

1985) and with the -1 frameshift in the retroviral gag-pol-type class (Jacks et al., 1988). Another sequence combination conforming to this rule is the passage of tRNA from its initial zero frame codon to a non-overlapping synonymous codon. This type of event, termed a tRNA hop (Weiss et al., 1987), has been observed with normal tRNAs and suppressor tRNAs (Falahee et al., 1988; O'Connor et al., 1989), and has been shown to be one component of the 50 nt. frame-jump across the coding gap of gene 60 of bacteriophage T4 (Huang et al., 1988; Weiss et al., 1990a).

The -1 frameshifts found in retroviral gene overlaps and the +1 frameshift found in the E.coli RF2 gene both utilize extensive flanking mRNA sequence context to increase the amount of frameshifting at a specific site. Investigation of these new examples has already revealed unexpected interplay between mRNA, ribosomes, and tRNA inside and outside of the decoding sites (Weiss et al., 1988; Jacks et al., 1988b; Brierly et al., 1989).

Figure 1 depicts the mRNA sequence features which contribute to maximal +1 frameshifting at the RF2 frameshift site. The amount of +1 frameshifting is between 30 and 50%, with the CUU-decoding leucyl-tRNA slipping +1, both in the natural gene (Craig et al., 1985) and in a synthetically-derived lacZ fusion (Weiss et al., 1987). When the CUU-U shift site is examined in a heterologous mRNA context, the detectable level of +1 frameshifting is < 0.2%, indicating that the mRNA context plays a major role (Weiss et al., 1987).

Genetic dissection of the flanking mRNA sequence has revealed two distinct elements. The 3' element (sequence feature 2b, Figure 1) is a simple stop codon located next to the codon at which the frameshifting tRNA initially decodes. In E.coli, any of the three stop codons can stimulate frame 'slipping' of a tRNA decoding strings of repetitive nucleotides (Weiss et al., 1987). This property may indicate a relatively slow step in the termination pathway prior to release factor binding (Curran and Yarus, 1989; Weiss et al., 1990b).

The second flanking element was shown to be an RNA:RNA hybrid (Weiss et al., 1988) between the AGGGGG mRNA sequence 4 nts. 5' of the frameshift site and nucleotides 1535-1540 of 16S

Sequence Features:

- 1 single slippery codon
- 2a 5' mRNA:rRNA hybrid, critical spacing
- 2b 3' stop codon

Figure 1. Multiple sequence features that contribute to the level of site-specific +1 frameshifting in the release factor 2 gene of *E. coli*.

Three elements determine the amount of +1 frameshifting at the RF2 frameshift site: a slippery codon, a 3' flanking stop codon and a 5' flanking mRNA:rRNA transient hybrid formation. Disruptions of the slippery codon (i.e., negated the ability of a well-decoded tRNA to base-pair effectively in an overlapping reading frame) reduce frameshifting by > 100-fold, while stop to sense alterations and removal or spacing changes of 5' Shine-Dalgarno sequence cause 10-20 fold reductions (Weiss et al., 1987).

rRNA ; essentially a Shine-Dalgarno interaction during the elongation phase. This observation implies a continuous cycle of hybridization and melting of the 3' end of 16S rRNA with the mRNA as the ribosome translocates along the message. The function of this cycle is unknown, but it can serve to dampen, as well as stimulate certain frameshift sites (Weiss et al., 1990b).

The -1 frameshifts first observed in retroviral gag-pol overlaps (Jacks and Varmus, 1985) constitute a widely distributed class of events. They are comprised of two major sequence features (Figure 2): a tandem set of 'slippery' codons at the frameshift site and a flanking 3' stimulating element. The hallmark of this class of -1 frameshifts is that effective offset base-pairing potential is required for the set of tandem codons and the frameshift occurs after the second codon has been correctly decoded in the zero frame.

- Sequence Features:**
- 1 tandem slippery codons
 - 2 3' mRNA structure (stem-loop or pseudoknot)

Figure 2. mRNA sequence features utilized by retroviral gag-pol overlaps and analogous high-level -1 frameshift sites.

Two essential elements are found in these -1 frameshift sites: a tandem slippery codon at the frameshift site and a flanking 3' mRNA structure. Both eukaryotic and prokaryotic ribosomes are able to respond to these elements.

The second sequence element found associated to various extent with these -1 frameshift sites are a 3' flanking element. The most impressive element found to date is an RNA pseudoknot, located 6 nucleotides 3' of the putative frameshift site in the F1/F2 overlap of the coronavirus IBV (Brierly et al., 1989). Potential stem-loop structures are located approximately 7 nucleotides from the putative frameshift sites in most viral examples, and compensating base-pair substitutions have implicated these directly in the Rous sarcoma virus gag-pol shift (Jacks et al., 1988).

When the eukaryotic viral sequences are translated in vivo by E.coli ribosomes, they are still capable of eliciting the same type of frameshift (Weiss et al., 1989). A simple C to G substitution at the MMTV gag-pro frameshift site (A-AAA-AAC to A-AAA-AAG) causes a 50% level of -1 frameshifting at this sequence by E.coli ribosomes, indicating a basic conservation of the tRNA:mRNA:ribosome interactions. The frameshifting rate of E.coli ribosomes also responds to 3' stem-loop structures, and one can speculate that the ribosomal process responsible for melting mRNA secondary structure of bacterial attenuators (Landick and Yanofsky, 1988) and translational control regions of

antibiotic resistance genes (Alexieva et al., 1988), is interacting with this 3' flanking element. Detailed interpretations of why the melting of mRNA secondary structure located at least 6 nts. 3' of the decoding sites should influence the position of the tandem tRNAs in the decoding sites have been proposed (Jacks et al., 1988; Weiss et al., 1989).

An enigma: the gene 60 50 nucleotide frame-jump

The discovery of an internal 50 nucleotide nontranslated coding gap within the coding region of gene 60 mRNA (Huang et al., 1988), revealed a new class of ribosomal frameshifts, which may more properly be termed 'frame-jumps'. The 50 nt. coding gap separates the first 46 codons from the last 114 codons of gene 60; these 160 discontinuous codons encode the 18 kd subunit of the bacteriophage T4 DNA topoisomerase. The ability of translating ribosomes to bypass the gap can be re-constructed in E.coli with gene 60-lacZ fusions, where the gap bypass efficiency in vivo approaches 100% (Weiss et al. 1990a). A mutational analysis of these gene 60-lacZ fusions has defined 5 key sequence features that contribute to high-level bypass (Figure 3). These features are: a segment of the nascent peptide translated from the sequence preceding the gap, a stop codon at the 5' junction, a short stem at the beginning of the gap, a duplicated codon flanking the gap and the distance between these two codons all contribute to gap bypass (Weiss et al., 1990a).

The sequence features in the coding gap region (features 2 through 5, Figure 3) suggest that the bypass mechanism may be akin to tRNA hopping. That is, the gly-tRNA initially decoding GGA⁴⁶ locates the 3' junction by dissociating from mRNA, passing over the gap and binding at the GGA codon situated 50 nts. away. The stop codon and short stem-loop may facilitate the initial dissociation from the 5' GGA codon. As yet unexplained are the optimal 50 nt. spacing between these two codons necessary for maximal bypass and the mechanism which supplies the impetus to the ribosome so that it may track 50 nts. along the mRNA.

Figure 3. Multiple sequence features contributing to the high-level ribosomal frame-jump observed in gene 60.

Five sequence elements necessary for maximal bypass of the 50 nt. coding gap listed. The order (1 through 5) indicates the relatively severity of inactivating mutations in the elements, with #1 being the most severely affected. This interpretation of coding gap bypass is based on a mutational analysis of gene 60-lacZ fusion expressed in E. coli (Weiss et al., 1990a).

The most unexpected sequence feature that has been found within the gene 60 sequence is the requirement for a cis-acting nascent peptide sequence centrally located in the 46 amino acid 5' coding region (Weiss et al., 1990a). Elimination of this sequence by phasing the ribosome across this region in an alternate frame decreases the bypass efficiency by nearly three orders of magnitude. The loss of gap bypass seen with the phase variants implicates amino acid residues 17 to 32 as activators of gap bypass, but does not indicate which features of the KKYKLQNNVRRSIKSSS sequence are important or indicate by what possible mechanism such a sequence could elicit the jumping over a 50 nt. section of mRNA.

Figure 4 lists the scores from a FASTA sequence similarity search of the 46 amino acid 5' peptide versus the NBRF protein sequence database, and Figure 5 displays a few chosen alignments.

(Peptide) FASTA of: Wai5seq.Pep from: 1 to: 46 March 24, 1990 22:15
 5' end of gene60
 TO: NBRF:* Sequences: 12,476 Symbols: 3,406,022 Word Size: 2

The best scores are:

init1 initn opt..

New:A24897	DNA topoisomerase II - Yeast (Schizosaccharom...	38	55	42
Protein:Mfnzb3	Matrix protein - Bovine parainfluenza vir...	51	51	54
Protein:Qgvz25	Hypothetical protein D-551 - Vaccinia vir...	46	46	53
New:S00111	Ribosomal protein L5 - Rat	45	45	52
New:A27380	Ribosomal protein L5 - Rat	45	45	52
Protein:Isectb	DNA topoisomerase (ATP-hydrolyzing) (EC 5...	33	44	38
New:A23807	30S ribosomal protein S13 - Escherichia coli	39	39	45
Protein:R3ec13	30S ribosomal protein S13 - Escherichia coli	39	39	45
Protein:Wmbe71	57K protein - Herpes simplex virus (type 1)	38	38	46
Protein:Sybycs	Carbamoyl-phosphate synthetase (EC 6.3.5...	38	38	42
New:A26596	Cell division control protein 25 - Yeast (Sac...	37	38	37
Protein:R3ec18	30S ribosomal protein S18 - Escherichia coli	38	38	39
Protein:Fovwv1	gag polyprotein - AIDS virus LV (lymphade...	38	38	46
Protein:Gnljvs	pol polyprotein - Visna lentivirus (strai...	38	38	40
Protein:Fovwa2	gag polyprotein - AIDS virus ARV-2 (AIDS-...	38	38	48
Protein:Fovwh3	gag polyprotein - AIDS virus HTLV-III (T-...	38	38	46
Protein:Fovwlv	gag polyprotein - AIDS virus LAV-1a (lymp...	38	38	46
New:A26480	Knob protein - Plasmodium falciparum (fragment)	37	37	42
New:A29454	Knob-associated histidine-rich protein precur...	37	37	42
New:A05205	Hypothetical protein 1708 - Common tobacco ch...	30	37	39
Protein:Mfnzsv	Matrix protein - Parainfluenza 1 virus (s...	37	37	42
New:A25630	DNA topoisomerase II - Yeast (Saccharomyces c...	37	37	63
Protein:Mfnzs	Matrix protein - Parainfluenza 1 virus	37	37	42
New:B28821	Phospholipase C (EC 3.1.4.3) III - Rat	31	36	32
Protein:Xqbs	Amidophosphoribosyltransferase (EC 2.4.2.14...	36	36	37
Protein:Rgeciy	Regulatory protein ilvY - Escherichia coli	36	36	41
Protein:R3nt15	Ribosomal protein S15 - Common tobacco ch...	36	36	37
Protein:P2wl11	Probable L2 protein - Papillomavirus (typ...	36	36	36
Protein:Tvbyq4	Transforming protein (ras) - Yeast (Sacch...	36	36	36
New:D24444	Hypothetical protein 4 (16S-23S rRNA spacer r...	36	36	36
New:A27787	Thyroid peroxidase - Human	35	35	37
New:A27416	Thyroid peroxidase (EC 1.11.1.8) - Pig	34	35	36
Protein:Ntsreb	Neurotoxin XI - Scorpion (Buthus occitanus)	35	35	35
Protein:R5bs2f	50S ribosomal protein L2 - Bacillus stea...	35	35	40
New:A29496	Cytochrome f precursor - Rice chloroplast	35	35	43

Figure 4. Protein sequence similarity search of the 46 amino acid 5' peptide from gene 60 versus the NBRF data base.

The score table from a FASTA search (Pearson and Lipman, 1988) of the National Biomedical Research Foundation (NBRF) protein sequence database (Release 21.0, 6/89) is shown. The PAM250 matrix was used in the second step of the comparison. The search was run on a VAX 8300 using the UWGCG software package (Devereux et al., 1984).

Ribosomal protein L5 - Rat

Gaps: 0 Quality: 21.40 Ratio: 0.465 Score: 21.40

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1 MKFVKIDSSSDMKKYKIQNNVRSIKSSSMNYANVAIMTDADHDG 46
| |||: . . . : | : . . . | | . | . . . : | . . . . .
1 MGFVKVVKNAKAYFKRYQVRRRRREGKTDYYARKRLVIQDKNKYNT 46

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30S ribosomal protein S13 - Escherichia coli

Gaps: 0 Quality: 22.80 Ratio: 0.518 Score: 22.80

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1 MKFVKIDSSSDMKKYKIQNNVRSIKSSSMNYANVAIMTDADHDH 44
: . . | | . . : : | : . . : | | . | . . . : : . : |
47 LSEGQIDTLRDEVAKFVVEGDLRREISMSIKRLMDLGCYRGLRH 90

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30S ribosomal protein S18 - Escherichia coli

Gaps: 0 Quality: 20.50 Ratio: 0.456 Score: 20.50

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1 MKFVKIDSSSDMKKYKIQNNVRSIKSSSMNYANVAIMTDADHDH 45
. | | : . . : | : . . : | . . : . . : . . : | . . :
7 RKFCRFTAQGVQEIDYKDIAITLKNYITESGKIVPSRITGTRAKYQ 51

```

core polypeptide (gag) p17-Human immunodeficiency virus I

Gaps: 0 Quality: 23.20 Ratio: 0.516 Score: 23.20

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2 KFKVIDSSSDMKKYKIQNNVRSIKSSSMNYANVAIMTDADHDG 46
| : | | . . . : | | | | : | : | . . . . . : | : . . .
15 KWEKIRLRPGGKKYKLGKLVWASRELERFAVNPGLLETSEGCRQ 59

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Figure 5. Pair-wise alignment of the 46 amino acid 5'peptide with three ribosomal proteins and the gag-encoded core polypeptide of HIV-1.

The PROFILE programs (UWGCG software package) were used to align the gene 60 5' peptide with a few selected high-scoring matches found with the FASTA search.

Besides the similarity to other type II topoisomerases, intriguing weak similarities are found with a number of ribosomal proteins (Rat L5, *E.coli* S13 and S18; Figure 5), and to retroviral gag-encoded core proteins. Such similarities and the net + charge of this segment (isoelectric pH=11.82) may indicate that this segment is an RNA binding module. The exact nature of the activation of gag bypass by this nascent chain remains to be determined.

Frameshift and frame-jump sites as control points

The apparent design of both the RF2 and retroviral frameshift sites seems sensible. The RF2 level in the cell can feedback on RF2 synthesis by competing with the frameshift at the stop codon (Craigén and Caskey, 1986; Weiss et al., 1990b). Most retroviruses gauge the ratio of gag and gag-pol polyproteins with the -1 frameshift events, and thus balance the production of gag-derived structural proteins and pol-derived enzymes found within the viral particle. The retroviral-type of -1 frameshift observed in some insertion elements may balance the ratio of transposase to transposition inhibitor (Sekine and Ohtsubo, 1989). Since slippery strings in these special contexts seem to be the

culprits in the majority of leaky frameshifts, careful pruning of these sequences from open reading frames would serve to minimize loss of normally elongating ribosomes.

The puzzle of why gene 60 carries a high-level ribosome jump is however quite unclear. There is no genetic evidence to implicate a regulatory function to the jump. Ribosomes do not normally skip over 50 nts. in the middle of translating messenger RNAs. The event observed in gene 60 is the first of its kind, although a potential 12 nt. in-frame jump has recently been postulated to occur from codons 4 to 8 within the carA mRNA from P.aeruginosa (Wong and Abdelal, 1990). Thus, other genes may also be taking advantage of the possibilities of high-level ribosome jumping for reasons yet unknown.

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