

Reprogramming the genetic code: The emerging role of ribosomal frameshifting in regulating cellular gene expression

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Reading frame maintenance is a critical property of ribosomes. However, a number of genetic elements have been described that can induce ribosomes to shift on mRNAs, the most well understood of which are a class that directs ribosomal slippage by one base in 5' (-1) direction. This is referred to as programmed -1 ribosomal frameshifting (-1 PRF). Recently, a new -1 PRF promoting element was serendipitously discovered in a study examining the effects of stretches of adenosines in the coding sequences of mRNAs. Here, we discuss this finding, recent studies describing how -1 PRF is used to control gene expression in eukaryotes, and how -1 PRF is itself regulated. The implications of dysregulation of -1 PRF on human health are examined, as are possible new areas in which novel -1 PRF promoting elements might be discovered.

Keywords:

■ cancer; frameshifting; miRNA; NMD; polyA track; pseudoknot; ribosome; ribosomopathy; SCA26; telomere; translation

DOI 10.1002/bies.201500131

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Abbreviations:

-1 PRF, programmed -1 ribosomal frameshifting; NMD, nonsense-mediated mRNA decay; NSD, "non-stop" decay; PTC, premature termination codon.

Introduction

We are living in a golden age of scientific discovery, from the detection of exoplanets and the near certainty of extraterrestrial life, to the visualization of atomic scale molecular machines in action. While new findings tend to be consistent with generally accepted theories, they also reveal interesting exceptions to the general rules. In so doing, they both further illuminate these rules, and help to reveal the deeper mysteries of the natural world. In this essay we discuss how the discovery of *cis*-acting mRNA elements that subvert normal mRNA decoding is adding a new dimension to our understanding of how cellular gene expression is regulated.

A quick tutorial on protein synthesis

mRNAs are decoded by ribosomes as groups of three contiguous nucleotides (codons) on messenger RNAs (mRNAs). Each codon specifies either an amino acid or, in three cases, instructions to stop protein synthesis. Ribosomes are programmed to identify the right place to start (initiation, usually at an AUG codon encoding methionine in eukaryotes and archaea and formyl-methionine in prokaryotes), and then proceed to decode the genetic information in the mRNA by marching (elongation) down the mRNA in the 5' to 3' direction 1 codon at a time until they reach one of the stop codons (termination). Central to this is that ribosomes must maintain the reading frame as defined by the initiation codon, in order to properly decode the information contained in the mRNA. Translational reading frame maintenance is an underappreciated area of research as compared to a large body of literature on e.g. mechanisms underlying tRNA charging by aminoacyl-tRNA synthetases, or the accurate decoding of codons [1]. From this, it follows that bad things must happen when ribosomes fail to maintain reading frame. And indeed, this is true ... with some exceptions.

PolyA tracts and mRNA decay

To explore these exceptions, we begin with a recent paper by Arthur and co-workers [2] describing why consecutive runs of A residues rarely occur in the protein coding regions of mRNAs, and their surprising elucidation of how such polyA tracts are used to regulate gene expression. Prior studies in nucleated (eukaryotic) cells had shown that if ribosomes bypass a normal stop codon they become stalled on the mRNA's polyA tail. This is presumably due to the fact that the AAA codon encodes the basic amino acid lysine, and the demonstrated ability of poly-basic polypeptides such as poly-lysine promote ribosome stalling [3, 4], presumably through their interactions with the negatively charged ribosomal exit tunnel [5]. The stalled ribosomes are recognized by a complex of proteins that remove the ribosome for recycling [6]. During this process, the complex also recruits an endonuclease which cleaves the mRNA and initiates its degradation. This is called “non-stop” decay (NSD) because the failure of ribosomes to stop where they are supposed to results in destruction of the mRNA (reviewed in [7]). While on the subject of mRNA decay, two additional mechanisms merit discussion. A second is initiated when ribosome stalling occurs in the protein coding sequence, typically due to strong mRNA structures that are difficult to unwind. Here, the same (or similar) machinery is recruited to save the ribosome and kill the message: this is called “no-go” decay (NGD) [8, 9]. Thirdly, if a ribosome encounters a stop codon in the wrong context e.g. far away from a polyA tail (called a premature termination codon, or PTC), mRNA degradation proceeds through an independent process called the nonsense-mediated mRNA decay pathway (NMD) (recently reviewed in [10]). Note that although the ribosome is at fault in these cases, it is the messenger that pays the price.

Arthur and co-workers mined sequence data to find that runs of polybasic amino acids are universally underrepresented in the protein coding regions of mRNAs. This engendered the hypothesis that these might be used as regulatory elements by acting as “translational attenuators” akin to the NSD process. Surprisingly however, only runs of polyA, but not repeated AAG codons (which also encodes poly-lysine) or repeated CGA or AGG (encoding poly-arginine), conferred strong translational attenuation effects. Thus, something other than basic amino acid mediated ribosome stalling had to be operating.

Slip sliding away

Thirty years ago, the HIV/AIDS epidemic was dominating the headlines and the virus was just beginning to be characterized. Elucidation of retroviral genomic sequences by many different groups revealed a novel feature: overlapping and mutually out of frame open reading frames. This soon led to the discovery of special “slippery” sequences able to program elongating ribosomes to slip from one reading frame to another in a process that is called programmed -1 ribosomal frameshifting (-1 PRF) [11]. In the intervening years, we and others have characterized the nature of these -1 PRF signals, demonstrating the importance of -1 PRF on virus propagation

by ensuring synthesis of the correct stoichiometries of viral proteins [12–14]. More recently, it has been recognized that ribosomal frameshifting and other forms of translational recoding are widely used in all three domains of life [15–18]. Here, we focus on -1 PRF in eukaryotes, where computational searches for “classic” -1 PRF signals suggested that up to 10% of genes may be regulated by this mechanism [19]. Counter-intuitively, unlike viruses in which -1 PRF is used to synthesize two (or more) proteins from a single mRNA (Fig. 1A), more than 99% of -1 PRF events were predicted to direct elongating ribosomes to PTCs (Fig. 1B). Follow up studies revealed that these “genomic” -1 PRF signals function as mRNA destabilizing elements through NMD from yeast to humans [20–22]. Thus, while -1 PRF generally serves to expand the genomic coding content of viruses, in eukaryotes it appears to be primarily employed as a post-transcriptional regulatory

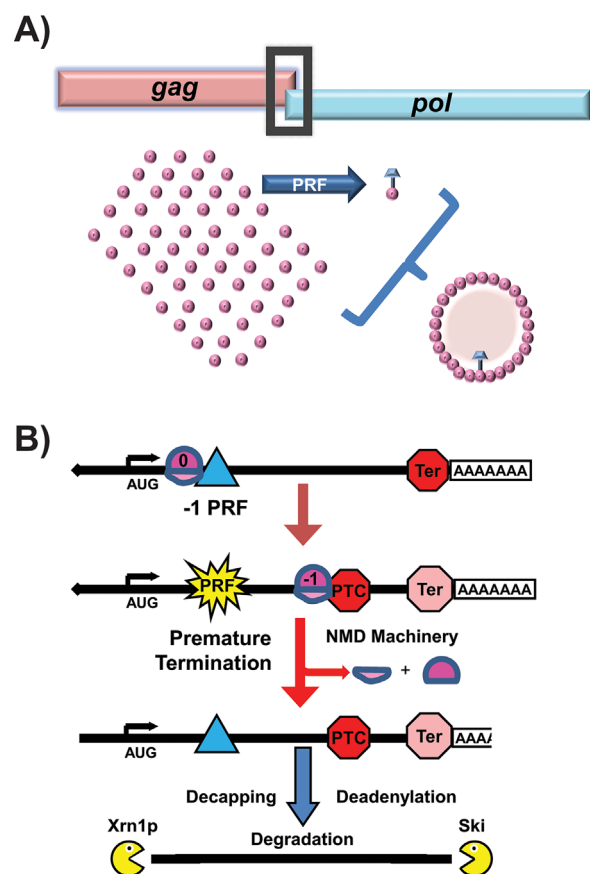


Figure 1. Frameshifting on viral compared to cellular mRNAs. **A:** In viruses, PRF events result in synthesis of C-terminally extended fusion proteins. In many virus families (e.g. Retroviridae, Totiviridae), rates of -1 PRF determine the stoichiometric ratios of capsid (pink Gag) to replicase (pink + blue Gag-pol) proteins. Correct ratios are critical for viral particle assembly. **B:** Canonical “genomic” -1 PRF signals or poly(A) tracts (blue triangle) can direct an elongating ribosome to a -1 frame premature termination codon (PTC). The recognition of the PTC by the ribosome results in activation of nonsense mediated mRNA decay (NMD) pathway and subsequent degradation of the transcript through a process of decapping and deadenylation followed by exonucleolytic degradation by Xrn1p (5′→3′) and the Ski complex (3′→5′).

mechanism. However, while classic -1 PRF signals require slippery stretches of nucleotides, slippage is greatly stimulated by strong downstream RNA structural elements that induce elongating ribosomes to pause at the slippery sequences. Interestingly, a strong RNA secondary structural element can also promote significant rates of -1 PRF even in absence of an upstream canonical slippery site, albeit to a lesser extent [22]. Whether the stimulatory elements actively help ribosomes to slip, or passively enhance kinetic partitioning between reading frames remains to be determined. We and others have also recently shown that -1 PRF can be regulated in a sequence-specific manner through interaction of -1 PRF signals with *trans*-acting nucleic acids e.g. naturally occurring miRNAs and synthetic oligonucleotides [21, 23–25]. However, while polyA is one of the allowable “slippery” sequences within the coding region of an mRNA, the surprising finding was that it can direct efficient -1 PRF in the absence of any other stimulating element. Indeed, Arthur and colleagues demonstrated that as few as 9 A’s in a row were able to promote a significant fraction of ribosomes to shift reading frame. In the context of naturally occurring polyA sequences, these were shown to direct ribosomes to PTCs, destabilizing mRNAs through NMD, thus limiting protein expression. The ability of these short polyA sequences to promote frameshifting at rates of ~10% in the absence of a downstream stimulatory structural element is rather surprising. While not discussed by the authors, we suggest that the presence of poly-lysine in the ribosome exit tunnel may cause ribosomes to pause over the slippery polyA sequence, thus enhancing their ability to kinetically partition into the -1 frame. If so, this suggests that at least two different -1 PRF mechanisms convergently evolved as mRNA destabilizing elements to control gene expression in eukaryotic cells. Additionally, Gene Ontology analysis of polyA track containing messages identified by Arthur et al. reveals that approximately 12% are located in mRNAs encoding *trans*-acting regulatory factors involved in stress response and apoptosis. While this suggests a regulatory role for these sequences, no suggestion for how such regulation may be effected has been presented. In addition, the fact that polyA sequences do not promote slippage into the +1 frame is also interesting: while not discussed by the authors, perhaps this observation is instructive about the fundamental nature of how ribosomes naturally maintain reading frame.

Regulation of gene expression by -1 PRF

In our studies, we have validated -1 PRF signals in mRNAs encoding proteins involved in numerous cellular processes, including telomere maintenance [22] and the immune response [21]. Critically, the availability of a set of sequences that direct -1 PRF at rates ranging from 1 to 70% enabled the relationship between rates of -1 PRF and mRNA abundance to be determined:

$$f(x) = e^{-0.05x}$$

where x = -1 PRF efficiency and mRNA abundance is a function (f) of x (Fig. 2). Since this is an inverse exponential relationship, small changes in frameshifting can have large

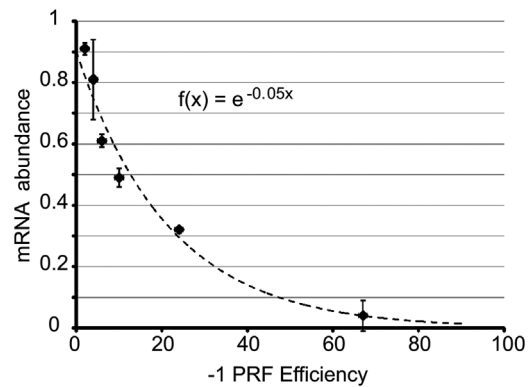


Figure 2. The relationship between frameshift efficiency and mRNA abundance. The mathematical relationship between -1 PRF efficiency and mRNA abundance was determined using frameshift signals derived from the yeast EST1, EST2, STN1, and CDC13 mRNAs. These were cloned into a reporter gene and cellular mRNA steady-state abundances were plotted relative to the abundance of the reporter without frameshift signals. Plotting of these data fit to the logarithmic function $f(x) = e^{-0.05x}$ (adapted from [22]).

effects on gene expression. This suggests that -1 PRF is a translational attenuation mechanism that functions to balance gene dosage. Intriguingly, most -1 PRF signals promote 1–10% frameshifting: this lies in the linear range of the plot where changes in -1 PRF efficiencies are predicted to promote the largest changes in mRNA abundances.

What might be the consequences of perturbing this delicate balance? In elegant studies using *B. subtilis*, Losick and co-workers have shown that switching between two morphological cell types is controlled not by the absolute numbers of regulatory molecules, but by their relative ratios [26]. This represents an important paradigmatic change: rather the Galilean quantitative numerical emphasis, it returns our understanding of biological regulation to the classical ratiometric Euclidian view. Curiously, included in the first report of yeast mutants in which -1 PRF was globally elevated was the observation that many of the mutants had temperature-dependent cell cycle defects [27]. Twenty years later, the basis for this was elucidated: in yeast, telomere maintenance is controlled by -1 PRF [22]. Global increases in -1 PRF imbalances the stoichiometries of key proteins that are either intrinsic to telomerase itself (Est1p and Est2p), or involved in telomerase recruitment to chromosome ends (Stn1p, Cdc13p). We hypothesize changes in the relative ratios of these proteins inhibits telomerase activity and/or recruitment to chromosome ends, triggering “checkpoint arrest” as cells work to repair this particular DNA synthesis defect before committing to cell division. This accounts for the observed cell cycle arrest phenotypes upon global dysregulation of -1 PRF. Notably, this phenomenon was also observed upon inhibition of NMD, consistent with the epistatic relationship of NMD to -1 PRF. Importantly, this places pressure on cells to select for mutations that bypass this quality control checkpoint, most commonly by “repairing” telomeres using the double stranded break repair apparatus. Unfortunately, this approach requires templating by homologous sequences, i.e. the ends of other chromosomes, which can lead to chromosome

fusion, breakage during mitosis, and eventually aneuploidy. Unpublished finding from our laboratory have recently validated -1 PRF signals in some human mRNAs encoding telomere maintenance proteins, suggesting the evolutionary conservation of -1 PRF in chromosome end maintenance.

Bad ribosomes

As noted above, we estimate that ~10% of nuclear encoded mRNAs harbor classic -1 PRF signals, and another ~2% harbor slippery polyA sequences; a respectable number of genes. Thus, it follows that defects in -1 PRF due to defective ribosomes may be significant drivers of disease. The importance of ribosomes and human health has emerged over the past decade through the emergence of a class of diseases collectively called Ribosomopathies [28]. Originally associated with genetically inherited anemias, it is becoming clear that mutations that affect ribosome biogenesis and/or ribosome function have dire consequences. Interestingly, while patients with classic ribosomopathies such as Shwachman–Bodian–Diamond syndrome and X-linked dyskeratosis congenita (X-DC) initially present with hypoproliferative cellular disorders e.g. anemias, should they survive this phase of the disease, they are at much higher risk of developing cancers of the same tissue bed, i.e. cellular hyper-proliferation. This seeming paradox is known in the field of hematology as Dameshek's Riddle [29]. Using X-DC as a model, we showed that rRNA hypopseudouridylation decreases the affinity of ribosomes for at least two classes of RNA ligands, internal ribosomal entry signals (IRES) and tRNAs [30]. While this leads to decreased expression of IRES containing mRNAs (emerging as an important driver of cancer [31]), this biochemical defect also renders tRNAs more likely to slip at -1 PRF signals. The effects of X-DC associated mutations on -1 PRF and gene expression is currently a topic of intense research. Unpublished findings from our laboratory also suggests that mutations associated with other classic ribosomopathies affect various aspects of translational fidelity, including -1 PRF, and hence gene expression.

An understanding of how somatically acquired mutations that affect translational reading frame maintenance may also underlie other cancers is beginning to take shape. Exome sequencing initially revealed a conserved mutation in the gene encoding ribosomal protein L10 (also known as uL16 [32]) in ~10% of T-cell acute lymphoblastic leukemias [33], and followup studies revealed that this mutation promotes globally increased rates of -1 PRF [34, 35]. Current efforts are aimed at characterizing how this affects gene expression and drives carcinogenesis. Additionally, while ribosomopathies are currently defined as diseases caused by defective ribosomes, it is not inconceivable that mutations that affect other components of the translational apparatus may also be pathogenic. Case in point: spinocerebellar ataxia 26 (SCA26) is an autosomal dominant disease caused by a mutation in EEF2, encoding the translational translocase eukaryotic elongation factor 2 (eEF2), which promotes increased rates of -1 PRF both in yeast [36], and in patient-derived cells (unpublished). Altered rates of ribosomal slippage may not only affect gene expression by altering mRNA abundances. The increased

expression of C-terminally truncated dead end polypeptides may also burden the cellular protein degradation apparatus. Indeed, yeast cells harboring the EEF2-SCA26 mutation show a more robust unfolded protein response (UPR) induction in response to antioxidant and heat shock challenges [36]. This may be of importance with regard to neurological disease in particular as Purkinje neurons are known to be vulnerable to a wide variety of molecular and cellular insults [37]. The links between -1 PRF and proteostatic insult represent a critical, underexplored area of investigation. Additionally, unlike the stringent quality control mechanisms governing ribosome biogenesis [38], no such control governing *trans*-acting factors like eEF2 are known. Thus, diseases associated with mutations in this class of proteins should be rare and may be expected to present as hypoproliferative only.

Sequence-specific regulation of frameshifting

If -1 PRF is widely used to control gene expression, then it stands to reason that it should be subject to regulation. However, given that global changes in -1 PRF appear to be deleterious, regulation of -1 PRF would have to be sequence-specific. microRNAs (miRNAs) and other non-coding RNAs naturally participate in sequence-specific interactions with mRNAs, and thus present the logical places to look for *trans*-acting regulators of individual -1 PRF signals. With this in mind, computational methods were used to identify two miRNAs that interact with and stimulate -1 PRF promoted by a sequence element in the mRNA encoding CCR5, a cytokine receptor that is used as a co-receptor for HIV-1 [21]. A series of genetic and biochemical experiments revealed that one of these, miR-1224, directly interacts with the CCR5 -1 PRF stimulating mRNA pseudoknot. Presumably, the interaction stabilizes the pseudoknot, rendering it more difficult for ribosomes to resolve. This would increase ribosome pause times at the slippery site, stimulating kinetic partitioning into the -1 frame. Theoretically, miRNAs may also have -1 PRF inhibitory activities by being able to destabilize -1 PRF promoting mRNA downstream elements. In support of this, siRNA knockdown of the cellular miRNA processing apparatus stimulated -1 PRF promoted by some frameshift signals, and inhibited -1 PRF promoted by others [21]. Non-coding RNA stimulation of -1 PRF at polyA sequences may also be possible. In support of this, hybridization of antisense linked nucleic acids (LNAs) immediately 3' of heptameric slippery sequences was sufficient to promote efficient -1 frameshifting in the absence of any other stimulatory element [39]. Natural attenuation of -1 PRF by stem-loop structures immediately 5' of coronavirus slippery sequences has also been reported [40], a phenomenon that can be replicated by hybridization of oligonucleotides complementary to sequences lying just upstream of slippery sites [41]. These studies establish the role of ncRNAs in regulating translational fidelity and suggest that regulation of -1 PRF may not be limited to miRNAs. Missing, however, is any hypothesis or model explaining how polyA-directed -1 PRF may be specifically regulated. The demonstration of protein-induced transactivation of frameshifting in porcine reproductive and respiratory syndrome virus [42]

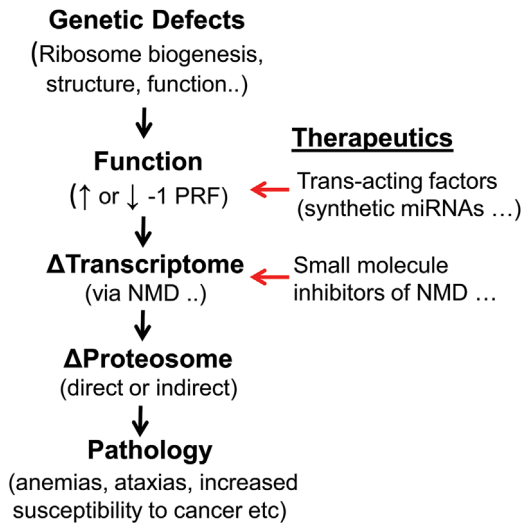


Figure 3. From genes to disease and points of therapeutic intervention. Mutations in genes that participate in translation that alter global rates of -1 PRF elicit downstream post-transcriptional surveillance pathways e.g. NMD that alter the transcriptome. This leads to altered gene expression (proteomic changes) and progression to disease states. Therapeutic approaches may include use of synthetic polynucleotide analogs (miRNAs and related derivatives) targeting specific -1 PRF signals designed to fine tune frameshifting rates. Given the epistatic relationship of NMD to -1 PRF, targeting this pathway using small molecule inhibitors presents another therapeutic modality.

may provide a clue in this respect; perhaps polyA-mediated -1 PRF may be regulated by polyA-binding proteins.

Conclusion and prospective

Arthur and co-workers serendipitously discovered that there is more than one way to program -1 ribosomal frameshifting. What other ribosomal frameshift promoting elements may be out there, and how might they be identified? An approach for discovering new -1 PRF signals that has worked particularly well with viruses and bacteria has been to first detect evolutionarily conserved reading frames and then, using molecular genetics tools, identify and characterize the translational recoding elements [16]. Mining of ribosome profiling data to pinpoint frameshifted ribosomes, and from there identifying the elements that made them shift reading frame presents a new and promising approach [21, 43]. The recent discovery of modified bases in mRNAs and their regulation [44, 45], raises the question of how these may affect the ability of ribosomes to maintain reading frame. Additionally, although we have known about mRNA editing for quite some time (reviewed in [46]), its role in creating or ablating -1 PRF signals remains completely unexplored. Furthermore, identifying the *trans*-acting factors (miRNAs, other ncRNAs and even proteins) that regulate specific -1 PRF signals, characterizing how their expression is regulated, and how dysregulation may be linked to disease is another open research area. Lastly, as outlined in Fig. 3, -1 PRF and

NMD present as therapeutic targets, not only with regard to viral diseases, e.g. HIV/AIDS, but also as a potential modality to fine tune and correct errors in gene expression, either using small molecules that target specific -1 PRF signals to correct the expression of specific genes (e.g. using synthetic RNA-like molecules) or using therapeutics that correct for changes in gene expression due to global defects in -1 PRF.

Acknowledgements

We would like to thank our co-workers, in particular Susan Baserga, Kim de Keersmaecker, Arlen Johnson, Davide Ruggero, John Woolford, Ian Brierley, John Atkins, and many others in the translational control field for participating in stimulating and creative discussions about the topics covered in this essay in an ongoing discussion over the past two decades. The discussion of Dr. Losick's findings in the context of Galilean versus Euclidian mathematical schemes was inspired by lectures by Drs. Losick and Mark A. Peterson (Department of Mathematics, Mount Holyoke College). We also wish to acknowledge members of the Dinman lab, past and present. This work was supported by grant to JDD from the National Institutes of Health (R01 HL119439, R01 GM117177).

The authors have declared no conflict of interest.

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