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Cell cycle control (and more) by programmed –1 ribosomal frameshifting: implications for disease and therapeutics

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Like most basic molecular mechanisms, programmed –1 ribosomal frameshifting (–1 PRF) was first identified in viruses. Early observations that global dysregulation of –1 PRF had deleterious effects on yeast cell growth suggested that –1 PRF may be used to control cellular gene expression, and the cell cycle in particular. Collection of sufficient numbers of viral –1 PRF signals coupled with advances in computer sciences enabled 2 complementary computational approaches to identify –1 PRF signals in free living organisms. The unexpected observation that almost all –1 PRF events on eukaryotic mRNAs direct ribosomes to premature termination codons engendered the hypothesis that –1 PRF signals post-transcriptionally regulate gene expression by functioning as mRNA destabilizing elements. Emerging research suggests that some human diseases are associated with global defects in –1 PRF. The recent discovery of –1 PRF signal-specific trans-acting regulators may provide insight into novel therapeutic strategies aimed at treating diseases caused by changes in gene expression patterns.

Keywords: aging, cancer, frameshifting, miRNA, pseudoknot, ribosomopathy, Ribosome, SCA26, telomere, translation

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Introduction

Cells regulate gene expression via diverse mechanisms. From mRNA transcription to protein degradation, many regulatory systems affect the timing, localization, and rate of each reaction. Gene expression is primarily concerned with the abundance and translational activity of mRNA; therefore expression is increased when a message is transcribed more rapidly, stabilized by the cell, or more

available to actively translating ribosomes. Increased mRNA degradation, decreased transcription, translational silencing, and the storage of mRNA are the hallmarks of decreased expression.

The center of this spectrum between mRNA synthesis and protein degradation is translation, the timely and high-fidelity process of bringing together mRNA, aminoacylated-tRNA, and the ribosome. Cellular functions are generally not impacted by sense errors, but nonsense, missense, and errors which change the reading frame tend to be deleterious; the translational apparatus has evolved to ensure that these are extremely rare. Simultaneously, the complex interplay of factors which effect translation suggest that the ribosome is a likely post-transcriptional regulation nexus of gene expression. Most evidence gathered thus far concentrates primarily on *cis*-acting elements in the 5' and 3' untranslated regions (UTRs) of mRNAs, and the *trans*-acting factors with which they interact. Coding sequences have more recently been examined for effects on post-transcriptional control, and multiple *cis*-acting mRNA elements have been found which cause elongating ribosomes to recode the mRNA sequence.^{1–4} In all kingdoms of life, these elements include, but are not limited to, sequences responsible for +1 and –1 programmed ribosomal frameshifting, termination codon suppression, stop-start elements, selenocysteine incorporation, and in archaea, pyrolysine incorporation.

Reading frame definition and maintenance

Translational reading frame maintenance is a primary determinant of the proteome. If the specificity of this process is lost or degraded, cells will almost certainly

die. This is a central point of attack by many antibiotics, which capitalize on small but distinct differences between bacterial and eukaryotic ribosomes.^{5,6} Reading frame is determined by recognition of a start codon by an initiator tRNA in the ribosome's decoding center and is maintained through the consistent translocation by 3 nucleotides during elongation. The three stop codons do not correspond to any tRNAs, this enables the release factor complex to initiate translation termination. Translational recoding comprises the spectrum of events which occur when canonical translation is disrupted. This ranges from mechanisms which subvert initiation,⁷ alter the equilibria of events during elongation,⁸ and affect the termination process⁹ generally resulting in suppression or reinitiation. This document mainly focuses on a particular recoding event called programmed -1 ribosomal frameshifting that occurs during elongation.

Programmed -1 Ribosomal Frameshifting

Programmed -1 ribosomal frameshifting (PRF) is a recoding mechanism historically associated with viruses¹⁰ and retrotransposons.^{11,12} This is due at least in part to the much smaller and compact nature of viral genomes and the relative simplicity in searching their kilobase scale genomes as opposed to megabase bacterial genomes or gigabase eukaryotic genomes. When the *gag* amber termination of the Rous sarcoma virus was found to be bypassed in favor of translation of a downstream -1 reading frame, 2 relatively simple and testable possibilities were considered: either a splicing event or the programmed shift of ribosomes into the new reading frame.¹⁰ Sequencing of the relevant region of the genome and *in-vitro* transcription/translation experiments supported the latter hypothesis and suggested that 'shifty tRNAs' caused the actual frameshift events. Shortly thereafter, reports described new RNA structures called pseudoknots, which when present in viral mRNAs could either repress translation¹³ or stimulate efficient ribosomal frameshifting.¹⁴ The Recode

databases^{15,16} (<http://recode.ucc.ie>) continue to categorize and describe these viral signals.

A PRF signal is defined as a *cis*-acting mRNA element that stochastically redirects translating ribosomes into an alternate reading frame. The most well characterized -1 PRF signals follow a relatively consistent pattern of stimulatory element proximally downstream of a group of weakly pairing bases (the "slippery heptamer") comprised of $N_x N_x N_x W_y W_y W_y H_z$; the spaces delineate the incoming reading frame, NWH refer to the IUPAC definitions, and xyz denote identical nucleotides. There is some debate regarding the relative contributions of the slippery heptamer, downstream stimulatory element, and the space between them; but all models of -1 PRF agree that the downstream mRNA structure causes elongating ribosomes to pause while tRNAs are positioned over the slippery site. The nature of the codon:anticodon interactions at the slippery site facilitates slippage of a fraction of paused ribosomes backward (5') by one base through pairing at the non-wobble positions. The weak homopolymer nucleotide sequences (poly-U or poly-A) are of particular interest in -1 PRF, as they are often coupled with pauses in translation in order to effect the frameshifting event.¹⁷ H-type mRNA pseudoknots are the most common stimulatory structure, but other structures, including proteins bound to stem-loops,¹⁸ variously sized stem-loops,¹⁹ and RNA triplexes²⁰ can also promote efficient frameshifting. The general mechanism and structure of a typical -1 PRF signal is diagrammed in Figure 1.

Genomic -1 PRF

Examination of the history of modern molecular genetics shows that most basic molecular mechanisms were first observed in viruses. Therefore, it was reasonable to hypothesize that -1 PRF is also used to control expression of cellular genes. Indeed, the serendipitous discoveries of -1 PRF signals of viral origin in the mammalian PEG10^{21,22} and Edr1²³ mRNAs suggested that more of these elements were hidden in eukaryotic genomes. Simultaneously, genetic studies in yeast

suggested that -1 PRF may play a role in cell cycle control.²⁴ Thus began the search for -1 PRF signals in eukaryotic genomes.

There are 2 complementary approaches when searching genome databases for potential frameshift signals. The first is to search for genes harboring conserved overlapping open reading frames.²⁵ This approach has been highly successful in identifying new viral -1 PRF signals, and conserved $+1$ PRF signals in ornithine decarboxylase genes.²⁶ However, while this enables identification of novel PRF signals, it enforces the assumption that frameshifting results in a new functional protein. The second method is to search for sequence motifs that conform to known PRF signals. Though limited to one class of signal, this method does not assume that frameshifting results in a C-terminal extension product.

The efforts of our laboratory have focused on this latter approach. In particular, -1 PRF was chosen because there are sufficient viral examples to enable the generation of heuristics. This is in contrast to $+1$ frameshifting, which appears to be idiosyncratic. The basic strategy is to perform a pattern-match based search for allowable heptameric slippery sequences followed by strong downstream structure; this search is NP-complete²⁷ and therefore computationally difficult. The initial study using this approach pressed the available CPU limits at the time, taking significant time for relatively small numbers of sequences.²⁸ Later searches against the yeast genome refined this strategy and used significantly greater computational resources, allowing the yeast genome to be exhaustively searched in months.²⁹ Further refinements, increases in memory/CPU, and larger computational resources made it possible to complete approximately one genome per week³⁰ along with comparisons against randomized sequences. Analysis of multiple genomes reveals that approximately 10% of annotated genes contain at least one high-confidence potential frameshift signal. A searchable database of predicted eukaryotic -1 PRF signals is available in the Predicted Ribosomal Frameshift Database (PRFdb, www.prfdb.umd.edu).³⁰

An unexpected result: cells use -1 PRF to control mRNA abundance

As noted above, a motif based search removes the assumption that frameshift events produce functional extended peptides. This led to the surprising observation that only 0.07% candidate -1 PRF containing sequences extend more than 30 codons beyond the frameshift event, regardless of the cellular genome examined (Fig. 2A). The observation that the vast majority of frameshift events direct translating ribosomes to premature termination codons engendered the hypothesis that -1 frameshift signals function as mRNA destabilizing elements through the nonsense mediated mRNA decay pathway (NMD)³¹ (Fig. 2B). This was initially validated in yeast cells using a well-defined viral frameshift signal and further analysis suggested a role for No-Go decay (NGD) as well.³² More recent studies in our laboratory demonstrate that this general rule is also true in human cells.³³

-1 PRF and gene expression

If $\sim 10\%$ of cellular mRNAs are controlled by -1 PRF, what is the biological significance of this phenomenon? As noted above, the first hint that -1 PRF may have a physiological role came from the observation that mutants that promote global increased rates of -1 PRF appeared to disrupt the cell cycle in yeast.³⁴ Indeed, a general observation in our laboratory over the past 2 decades has been that mutations that globally alter rates of -1 PRF compromise cell growth and viability.³⁵

The serendipitous discovery of a $+1$ PRF signal in the yeast EST3 mRNA, which encodes a component of telomerase,³⁶ prompted a search the PRFdb for -1 PRF signals in additional mRNAs encoding proteins involved in telomere maintenance. Operational -1 PRF signals (defined as promoting $\geq 1\%$ frameshifting) were identified in 4 mRNAs encoding proteins critical for yeast telomere maintenance. These are: EST2, encoding the reverse transcriptase component of telomerase; EST1, encoding the protein that “docks” telomerase to chromosome ends; and STN1 and CDC13 mRNAs, which encode proteins involved in recruiting telomerase to

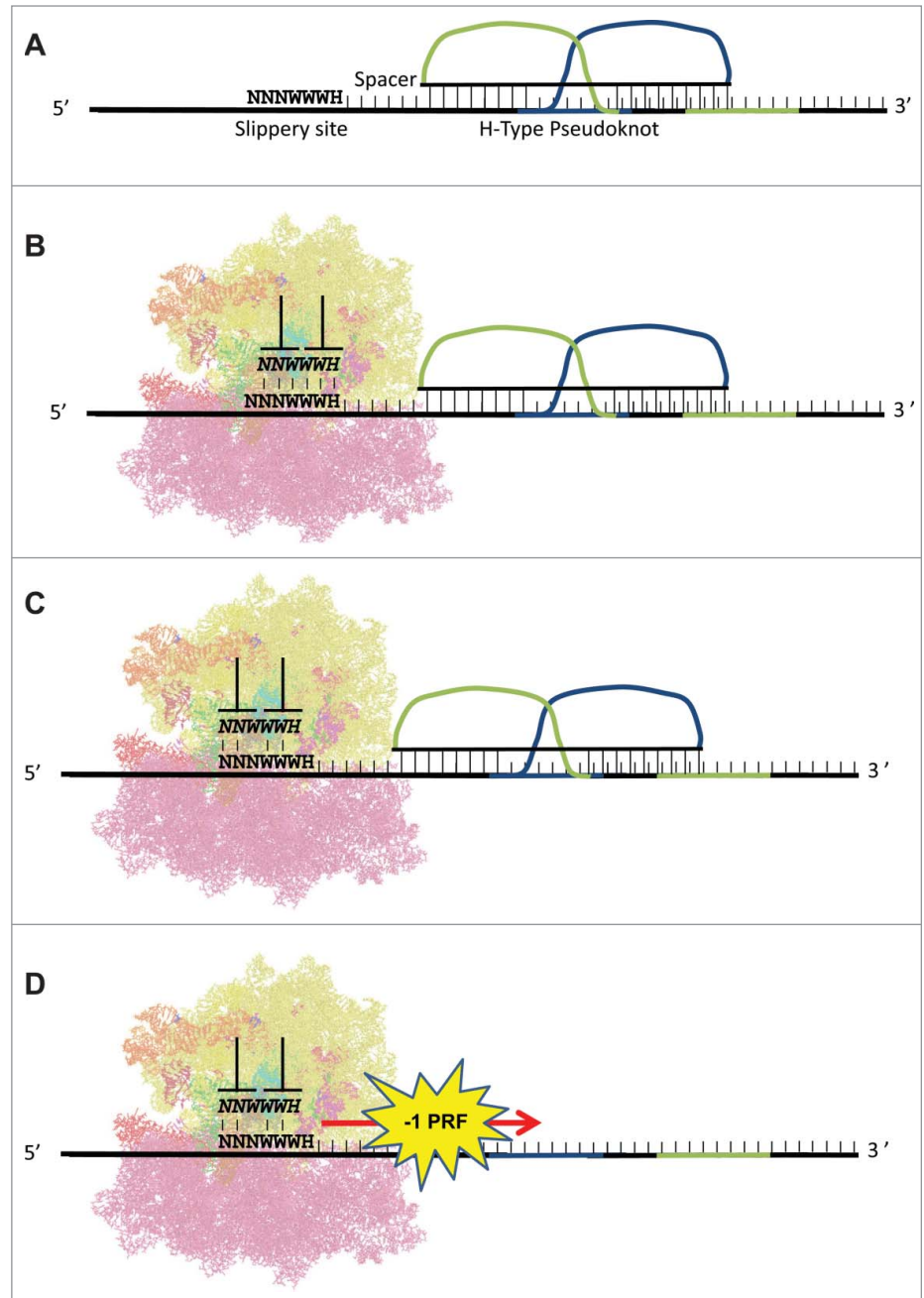


Figure 1. -1 PRF signals: structure and mechanism. (A) A typical -1 PRF signal is composed of 3 elements. 1) a heptameric “slippery site,” 2) a short spacer, and 3) a stable mRNA structure, e.g., an H-type pseudoknot. (B) The pseudoknot forces an elongating ribosome to pause with its A- and P-site tRNAs positioned at the slippery site in the 0-frame. (C) Slippage of the tRNAs by one base in the 5' (-1) direction enables non-wobble base pairing. (D) The ribosome denatures the pseudoknot, and translation elongation resumes in the -1 reading frame.

shortened telomeres. These were all shown to function as NMD-dependent mRNA destabilizing elements. The wide range of -1 PRF efficiencies (from 2% - 70%) promoted by these elements enabled characterization of a simple exponential decay function between -1

PRF efficiency and mRNA destabilizing activity:

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

where x denotes PRF efficiency and mRNA abundance is a function of x .

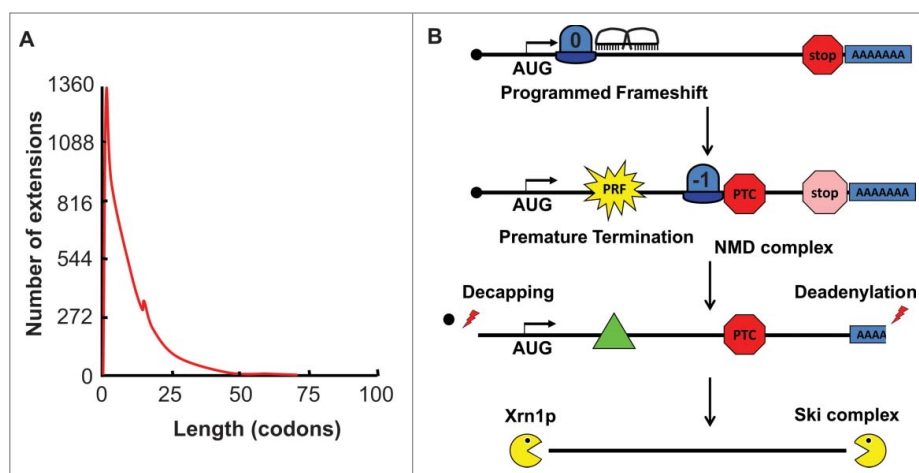


Figure 2. -1 PRF signals function as mRNA destabilizing elements. **(A)** Data from the programmed -1 ribosomal frameshift database (prfdb.umd.edu) plotting the number of -1 frame encoded C-terminal extensions (y-axis) versus their lengths in codons (x-axis) reveals that $>99\%$ of -1 PRF events direct ribosomes to termination codons within 30 codons. **(B)** Model: a -1 PRF event directs a ribosome to a premature termination codon. This triggers recruitment of the Nonsense Mediated mRNA Decay (NMD) complex to the mRNA, clearing the ribosome and initiating deadenylation of the 3' end followed by decapping of the 5' end. The mRNA then becomes a substrate for exonucleolytic degradation.

Abrogation of -1 PRF in the EST2 mRNA (leading to increased expression of this protein) yielded cells with telomeres of intermediate length, consistent with prior studies showing similar effects upon overexpression of this gene, or STN1 or CDC13.³⁷⁻⁴⁰ Importantly, abrogation of NMD resulted in cells with very short telomeres, consistent with NMD being epistatic to -1 PRF. Microscopic examination of these cells revealed that a large fraction were arrested at the G2/M boundary characterized by large mother cells attached to equally large daughter cells. Indeed, many of these cells had additional buds, characteristic of cell cycle “escape” mutants. In unpublished studies, operational frameshift signals have been identified in at least 2 human messages encoding proteins required for telomere maintenance; suggesting that -1 PRF may also play a role in human telomere maintenance and aging.

Model: how -1 PRF may control telomere length

In yeast, telomerase abundance is strictly limited: it is estimated that diploid cells, which contain 64 chromosome ends, only contain ~ 29 telomerase molecules,⁴¹ consistent with observations that

limitation of telomerase levels is required for telomere length homeostasis.⁴² Current models^{43,44} posit that telomeres exist in a range of states, from long, and fully capped (by Rap1p, Rif2p, Rif1p trimers) to short and uncapped, and that the small fraction of short uncapped telomeres present in any given cell cycle are preferentially repaired. As shown in **Figure 3**, as telomeres age, they progressively shorten, and at some point reach an intermediate, uncapped status. This recruits a complex containing the MRX complex (Mre11p, Rad50p, Xrs2p) plus Tel1p, which in turn recruits the CST complex (Cdc13p, Stn1p and Ten1), inducing checkpoint arrest at the G2/M boundary. Phosphorylation of Cdc13p by Tel1p enables recruitment of telomerase through Est1p, stimulating telomerase repair, and releasing cells from checkpoint arrest. Failure to recruit telomerase leads to further telomere shortening, where they eventually resemble double-stranded breaks (DSB). These short telomeres recruit the DSB repair machinery, resulting in strong checkpoint arrest at the G2/M boundary. Eventually, these short telomeres are maintained by this machinery, resulting in telomere end joining, and bypass of checkpoint arrest, i.e. multiply budded cells.

The net effect is to “immortalize” telomeres, resulting in longer lifespans, but at the cost of genome integrity. As shown in **Figure 3**, we propose that -1 PRF is used to maintain the correct stoichiometric ratios of telomerase components critical for telomerase recruitment. Changes in the expression of any one of these components, e.g. by abrogating -1 PRF in EST2 or overexpressing any single component, has dominant-negative effects on telomerase recruitment resulting in the observed increased rates of telomere shortening, consistent with the intermediate telomere lengths observed in these mutants. We further propose that changing the expression of all of the -1 PRF containing mRNAs, e.g., by globally changing rates of -1 PRF or by inactivation of NMD, has an even more dramatic effect, accounting for the very short telomeres observed in these classes of mutants.

Regulation of -1 PRF

If -1 PRF is normally employed to control gene expression, it stands to reason that -1 PRF itself should be subject to regulation. As suggested above, since global changes in -1 PRF tend to be detrimental to cells, regulation of -1 PRF should be sequence-specific. Given that -1 PRF is directed by *cis*-acting elements in mRNAs, sequence-specific interactions could be mediated by either base-pairing interactions with *trans*-acting RNAs, or by highly specific interactions with *trans*-acting proteins. Indeed, examples of both cases have been recently documented. The human CCR5 mRNA harbors a -1 PRF signal that functions as an mRNA destabilizing element by directing elongating ribosomes to premature termination codons, and we recently demonstrated that sequence specific interactions between this element and at least 2 micro-RNAs (miRNAs) promote increased rates of -1 PRF.³³ Mapping of the miRNA/ -1 PRF signal interaction suggested that formation of an RNA-triplex structure stabilizes the frameshift-stimulating mRNA pseudoknot, leading to increased ribosome pause times at the slippery sequence, further enhancing frameshifting. With this in mind, it is also possible that *trans*-acting RNAs that destabilize -1 PRF stimulating pseudoknots may also exist, i.e., these

Emerging evidence for a role of -1 PRF in human disease

The diagram illustrates the pathways of telomere uncapping and the resulting telomere maintenance outcomes. It is divided into three main sections: Capped, Uncapped, and DSB-like.

Capped: The telomere is shown with a double-strand structure. The 3' end of the top strand is capped by a complex of proteins: Rf1 (orange), Rf2 (yellow), and Rap1 (purple).

Uncapped: The telomere is shown with the 3' end of the top strand uncapped. The uncapping process involves the removal of the Rf1/Rf2/Rap1 complex. This leads to the recruitment of the MRX complex (Mre11, Rad50, Rap80) and the TSC complex (Tel1, Mps1, Chk2). The TSC complex then recruits the Est1 complex (Est1, Est2, Est3) and the TLC1 complex (TLC1, POT1, TPP1, TRF1, TRF2).

DSB-like: The telomere is shown with a double-strand break (DSB) at the 3' end of the top strand. The DSB is formed by the action of the MRX complex and the TSC complex. The DSB is then repaired by the Ddc1 complex (Ddc1, Rad17, Mec3, Rad9, Mec1). This leads to a checkpoint arrest, which is then bypassed by a crisis/checkpoint bypass mechanism.

Outcomes: The diagram shows two main pathways for telomere maintenance:

- Normal:** This pathway involves the recruitment/activation of Est1, 2, and Stn1, Cdc13 (NMD). This leads to the recruitment/activation of all 3 proteins (Stn1, Cdc13, NMD). This results in Tel. Maint. By DSB Repair.
- Uncapped:** This pathway involves the recruitment/activation of Est1, 2, and Stn1, Cdc13 (NMD). This leads to the recruitment/activation of all 3 proteins (Stn1, Cdc13, NMD). This results in Tel. Maint. By DSB Repair.

Consequences: The diagram shows that the uncapping of the telomere leads to a crisis/checkpoint bypass, which results in a rate of tel. shortening, a time to 'crisis' & DSB tel. maint., and an apparent lifespan.

Figure 3. Model: telomerase recruitment to uncapped telomeres is controlled by the relative stoichiometries of telomerase components in yeast. Top left depicts a fully capped telomere. As telomeres shorten, they become uncapped (middle left), recruiting the MRX-Tel1p complex, which in turn recruits the CST complex to the telomere end. Phosphorylation of Cdc13p by Tel1p recruits telomerase via Est1p. Est2p is the reverse transcriptase component of telomerase. If telomeres continue to shorten, they resemble chromosomes with double stranded breaks (DSB-like, lower left), recruiting DNA repair machinery. This results in cell growth arrest at checkpoint (G2/M). If cells cannot repair the defect, they undergo “crisis” and a subpopulation will bypass arrest, maintaining their chromosome ends by DSB repair. Operational -1 PRF signals have been identified in the STN1, CDC13, EST1 and EST2 mRNAs. We propose that their relative abundances are controlled by -1 PRF. In optimal conditions, precisely controlled rates of -1 PRF ensures that these proteins are present in the correct stoichiometries, maximizing telomere repair (bold up arrow), and minimizing progression to the DSB-like state. When expression of any one of these genes is altered, e.g. telomerase recruitment is less efficient and more telomeres progress more rapidly to the DSB-like state. When expression of all 4 are altered, e.g., by global changes in -1 PRF or by abrogation of NMD, telomeres progress rapidly to the DSB-like state.

patients with T-cell lymphoblastic leukemia (T-ALL) also promotes increased rates of -1 PRF (by promoting decreased ribosomal affinity for aminoacyl-tRNA) provides evidence that somatically acquired mutations that affect -1 PRF may contribute to at least some cancers.⁵¹

Like many basic molecular regulatory mechanisms, while -1 PRF was discovered in viruses it has now been found to be involved in the expression of a significant number of eukaryotic genes. Surprisingly, unlike viruses, where -1 PRF is used to expand the genomic coding content, it appears that -1 PRF signals are used to post-transcriptionally regulate gene expression by functioning as mRNA destabilizing elements. Emerging evidence

176

continue to guide a diverse set of research efforts into the future.

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