Translational control by 5′-untranslated regions of eukaryotic mRNAs

Alan G. Hinnebusch,[1] Ivaylo P. Ivanov,[1] Nahum Sonenberg[2]*

The eukaryotic 5′ untranslated region (UTR) is critical for ribosome recruitment to the messenger RNA (mRNA) and start codon choice and plays a major role in the control of translation efficiency and shaping the cellular proteome. The ribosomal initiation complex is assembled on the mRNA via a cap-dependent or cap-independent mechanism. We describe various mechanisms controlling ribosome scanning and initiation codon selection by 5′ upstream open reading frames, translation initiation factors, and primary and secondary structures of the 5′UTR, including particular sequence motifs. We also discuss translational control via phosphorylation of eukaryotic initiation factor 2, which is implicated in learning and memory, neurodegenerative diseases, and cancer.

Most eukaryotic mRNAs are translated by the scanning mechanism, which begins with assembly of a 43S preinitiation complex (PIC), containing methionyl-initiator tRNA (Met-tRNA$_i$) in a ternary complex (TC) with guanosine triphosphate (GTP)–bound eukaryotic initiation factor 2 (eIF2). The 43S PIC assembly is stimulated by eIFs 1, 1A, 3, and 5 (Fig. 1). Its subsequent attachment to mRNA at the m^{7}G-capped 5′ end is facilitated by the eIF4F complex—composed of cap-binding protein eIF4E, eIF4G, and RNA helicase eIF4A—and by poly(A)-binding protein (PABP). The PIC scans the mRNA 5′ untranslated region (UTR) for an AUG nucleotide triplet start codon using complementarity with the anticodon of Met-tRNA$_i$. AUG recognition evokes hydrolysis of the GTP bound to eIF2 to produce a stable 48S PIC. Release of eIF2-GDP is followed by joining of the large (60S) ribosome subunit, catalyzed by eIF5B, to produce an 80S initiation complex ready to begin protein synthesis (Fig. 1) (1). There are exceptions to the scanning mechanism in which PICs are recruited by specialized sequences in the 5′UTR, called internal ribosome entry sites (IRESs).

The scanning mechanism of translation initiation

The nature of scanning, its 5′ to 3′ directionality, dictates that the initiation codon is frequently the AUG triplet closest to the 5′ end, encountered first by the scanning PIC. The first AUG can be skipped when it is flanked by an unfavorable sequence—a process termed "leaky scanning"—to use a downstream AUG. A favorable sequence context in mammals is the "Kozak consensus,"

5′ (A/G)CCAUGG 3′ (2). Although not always the same in plants and fungi, a purine at the –3 position from the AUG both is conserved and functionally predominates over other positions in all organisms (1). When an upstream AUG (uAUG) is in-frame with a downstream AUG without an intervening stop codon, leaky scanning may occur at some frequency to allow production of two protein isomers differing only by an N-terminal extension, with the longer form often targeted to a particular cellular compartment. If the uAUG is followed by a stop codon in the same open reading frame (ORF), then translation of the upstream ORF (uORF) will attenuate translation of the downstream main ORF, because reinitiation is generally inefficient (Fig. 2A). Some uORFs inhibit downstream translation primarily because ribosomes stall during their translation and create a roadblock to scanning PICs that bypass the uORF start codon (Fig. 2B). These principles account for the fact that polycistronic mRNAs, common in bacteria, are rare in eukaryotes (1).

"Near-cognate" triplets, differing from AUG by a single base, can be selected by the scanning PIC but with lower frequencies, owing to the mismatch with the anticodon of tRNA$_i$ and attendant destabilization of the 48S PIC. NUG (N is any nucleotide) triplets generally function the best, whereas A(A/G)G triplets are the worst, and the use of near-cognates relies more heavily than AUG on optimal context (1). Although CUG codons are usually decoded by Met-tRNA$_i$, leucyl-tRNA^{Leu} can be engaged by a scanning PIC in a manner requiring the noncanonical initiation factor eIF2A but not eIF2. This occurs in the synthesis of antigenic precursors for loading on major histocompatibility complex molecules (3).

Multiple eIFs, structural elements of tRNA$_i$, and both rRNA and protein components of the 40S subunit participate in discrimination between AUGs and non-AUG triplets as start codons, and good versus poor Kozak context, by the scanning PIC (1). eIF1 and eIF5 have opposing effects, with
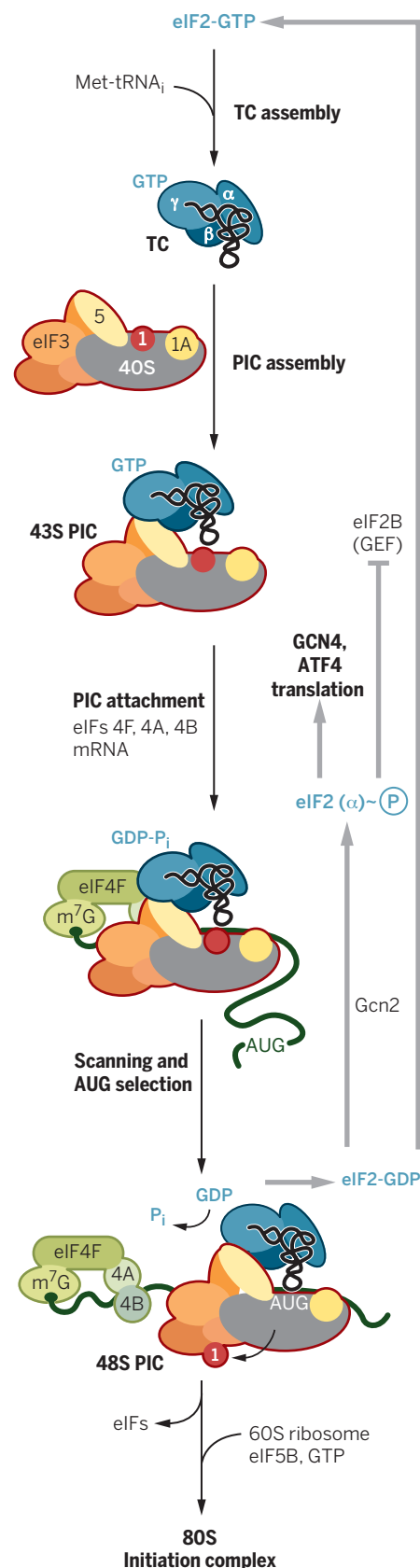
[1]Group on Cell Regulation and Development, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA. [2]Department of Biochemistry and Goodman Cancer Centre, McGill University, Montreal, Quebec H3A 1A3, Canada.
*Corresponding author. Email: nahum.sonenberg@mcgill.ca

Fig. 1. The scanning mechanism of translation initiation. The simpler 5-subunit version of budding yeast eIF3 is depicted.

eIF1 promoting scanning and blocking recognition of non-AUGs and AUGs in poor context and eIF5 antagonizing eIF1 function. These activities are exploited for autoregulation and cross-regulation of eIF1/eIF5 expression in most eukaryotes (4), because the eIF1 AUG is in weak context and poorly recognized unless eIF1 levels drop below a certain threshold (5). Initiation at the eIF5 start codon is impaired by an uORF whose AUG is in weak context and hence efficiently bypassed by leaky scanning only at low eIF5 (or high eIF1) levels (Fig. 3A) (4). Yeast mutants of these and other initiation factors (eIF1A, eIF2 subunits, and eIF3c) can increase or decrease discrimination against suboptimal start codons (1, 6). There is a potential for regulating such initiation events through posttranslational modifications of these factors or with small molecules.

Based on studies in yeast, in which dramatically lengthening the 5′UTR conferred no reduction in translational efficiency, it appears that the scanning PIC is highly processive (7). However, an excessively short 5′UTR [≤20 nucleotides (nt)] is generally detrimental and can evoke leaky scanning (1, 8). Indeed, genome-wide mapping of yeast 5′UTRs identified many mRNAs with short 5′UTRs exhibiting lower-than-average translational efficiency (TEs) (9). Leaky scanning induced by short 5′UTRs allows production of different isoforms differing at the N termini from the same mRNA (1, 10). In contrast, the mammalian 5′UTR element translation initiator of short 5′UTRs (TISU) allows cap-dependent but scanning-independent initiation on mRNAs with 5′UTRs as short as 5 nt. Although not requiring eIF4A, TISU's function paradoxically depends on eIF1 (11), which normally blocks selection of AUGs too close to the cap (8). mRNAs encoding mitochondrial proteins are enriched in TISU, which appears to confer maintenance of translation at low energy levels (11).

Translational control by 5′UTR structure

Secondary structures in the 5′UTR can also influence the initiation efficiency of suboptimal start codons. A strong stem-loop (SL) structure just downstream of the start codon will stall the scanning 40S subunit, increasing its "dwell time" and thus decreasing the probability of leaky scanning through near-cognates or AUG triplets in poor context (12).

Although a precise SL-AUG spacing is required for the SL stimulatory effect, mRNA structures of sufficient stability inhibit all scanning-dependent initiation downstream (1). DEAD-box adenosine triphosphate (ATP)–dependent RNA helicases can overcome SL structural impediments, and they might be specialized for certain types or locations of mRNA structures. The fact that eIF4A is recruited to the mRNA 5′ end and activated as a component of eIF4F positions eIF4A to facilitate PIC attachment near the cap to initiate scanning at the mRNA 5′ end (1). eIF4E overexpression preferentially stimulates translation of mRNAs containing excessive secondary structure, implying that eIF4F is limiting for translation of mRNAs with structured leaders (13). Mammalian DHX29 and the yeast homolog of DDX3 (Ded1) appear to be crucial for resolving stable structures distal from the cap that impede scanning (14). Indeed, genome-wide analysis of TEs in Ded1 and eIF4A yeast mutants revealed that Ded1-hyperdependent genes tend to have atypically long and structured 5′UTRs, whereas eIF4A contributes more equally to translation of all mRNAs (15). This differs in mammals, where eIF4A-dependence is conferred by long 5′ UTR sequences capable of forming stable secondary structure (16) or G-quadruplex structures (17). Moreover, mammalian mRNAs containing 5′UTR secondary structure are hyperdependent on eIF4A for translation in vitro (18). Cap-proximal structures can also impede eIF4F binding to the cap (19), and DDX3 was implicated in resolving cap-proximal SLs to enhance eIF4F recruitment (20).

Analogous to the inhibitory effects of cap-proximal SL elements, a paradigm of translational control in mammals involves formation of an mRNA-protein complex composed of the iron regulatory protein (IRP) and a cap-proximal SL known as the iron response element, which blocks 43S attachment to mRNAs encoding ferritin or other iron metabolism proteins in iron-deprived cells (21).

Translational control by uORFs

Genome-wide sequencing of 5′UTRs reveals that uORFs are pervasive, occurring in ~50% of mammalian mRNAs, and there is evidence from ribosome footprint profiling that a sizable fraction of uORFs are translated (22–24), although only a small fraction produces peptides sufficiently abundant and stable for detection (25). It is likely that ribosome occupancies of uORFs detected in certain profiling experiments overestimate their TEs in cells (26, 27). This is especially true for uORFs initiated by near-cognates under conditions where bulk protein synthesis is diminished, where their representation is substantially elevated compared with their use as start sites for main ORFs. However, the facts that the occurrence of AUG-initiated uORFs is below the frequency predicted by chance; that, when present, their start codons tend to be in poor initiation context; that their occurrence and translation is associated with below-average TEs for the downstream ORFs genome-wide; and that they show evidence of evolutionary sequence conservation are good indicators that AUG-initiated uORFs function broadly to throttle down translation initiation, whereas the same evidence is lacking for most non-AUG–initiated uORFs (9, 24, 28, 29). Regulation via uORFs is likely coupled to transcriptional control in yeast meiosis, where the transcription start sites of certain genes shift upstream to include one or more AUG-initiated uORFs, which is accompanied by diminished TE of the downstream ORFs (29). Termination at an uORF stop codon can elicit the same mRNA destabilization evoked by the nonsense-mediated decay pathway at premature termination codons in ORFs, magnifying the inhibitory effects of uORFs (9, 30).

Despite their widespread occurrence, direct evidence that particular uORFs inhibit translation of downstream ORFs exists only for a relatively small number of genes, with two primary control mechanisms at play. For one class of regulatory uORFs, the encoded peptide acts to stall the elongating 80S ribosome engaged in its synthesis at or near the uORF stop codon, creating a "roadblock" to scanning PICs that leaky-scanned the uORF AUG codon (Fig. 2B). This roadblock can be modulated by ligands to
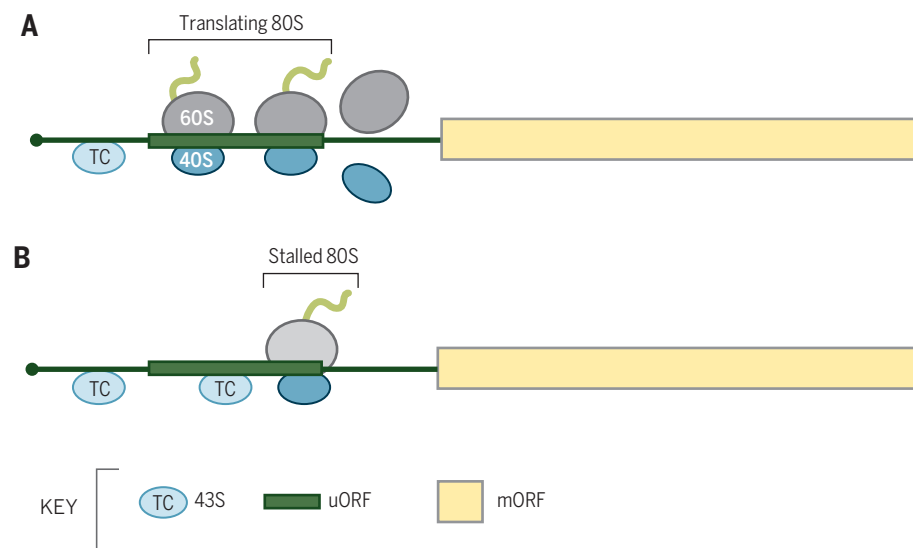

Fig. 2. Mechanisms of translational control by short uORFs. (**A**) The 43S PICs scanning from the mRNA 5′ end translate the uORF (as 80S ribosomes), and free subunits dissociate from the mRNA after termination, preventing translation of the main ORF (mORF). (**B**) The 80S ribosomes are stalled during elongation or termination by the uORF-encoded attenuator peptide and impose a barrier to scanning 43S PICs that leaky-scan the uORF start codon, preventing translation of the mORF. Stalling is modulated by small molecules.

achieve translational control—e.g., arginine for yeast *CPA1* and *Neurospora crassa arg-2* attenuator peptides (*31, 32*) or spermidine for *ADM1* (*33, 34*).

An encoded peptide sequence is irrelevant for a second class of regulatory uORFs that function only to waylay scanning PICs from the downstream ORF start codon (Fig. 2A). That the barrier imposed by such uORFs is generally overcome by leaky scanning is suggested by genome-wide data indicating that uORFs whose AUG codons better conform to the Kozak consensus are more inhibitory (*23, 28*). Also, that upstream start codons tend to be near-cognates or AUGs in poor context should favor leaky scanning (*23*). Leaky scanning of an inhibitory uORF, through an unknown mechanism, is increased under stress conditions that evoke phosphorylation of eIF2 on serine-51 of its α-subunit eIF2(αP) (Fig. 3A) (*35*). This applies to GADD34, a targeting subunit for protein phosphatase-1 that dephosphorylates eIF2α, enabling autoregulation of eIF2(αP) accumulation (*36*). Phosphorylation of eIF2α converts eIF2-GDP into a competitive inhibitor of the guanine nucleotide exchange factor eIF2B and thereby decreases TC assembly (Fig. 1) (*37*). This might allow a fraction of PICs scanning from the cap to reach the uORF without harboring the TC, bypass the uAUG (owing to the absence of Met-tRNA$_i$), and bind TC while scanning the remainder of the 5′UTR, and initiate at the main ORF. Alternatively, phosphorylation might also alter eIF2 function in start codon recognition to allow leaky scanning even with TC bound to the PIC.

The presence of multiple uORFs can greatly amplify the effect of eIF2α phosphorylation on leaky scanning, as demonstrated first for yeast *GCN4* (*37*) and subsequently mammalian *ATF4* and *ATF5* (*38, 39*), which encode transcription factors instrumental in responding to stresses that activate eIF2α kinases, such as amino acid deprivation for kinase Gcn2 (Fig. 1) and endoplasmic reticulum stress for protein kinase R–like endoplasmic reticulum kinase (PERK). The first (uORF1) is translated by most scanning PICs and optimized to allow a fraction of 40*S* ribosomes to remain attached to the 5′UTR and reinitiate downstream (*37*). For *GCN4* uORF1, sequences/structures upstream of the uORF functionally interact with the a-subunit of eIF3 and AU-rich sequences 3′ of the uORF stop codon to allow scanning to resume (*40*). With abundant TC in nonstressed cells, "rescanning" PICs rebind TC rapidly and efficiently reinitiate at the downstream uORF(s), optimized to evict posttermination 40*S* subunits from the mRNA and prevent translation of the downstream main ORF. The decreased TC levels evoked by eIF2α phosphorylation allow a fraction of rescanning PICs to rebind TC only after leaky scanning the inhibitory uORFs, and initiate downstream at the ORF instead (Fig. 3B). Because of minimal leaky scanning of the inhibitory uORFs in nonstressed cells, owing to their optimum context, only a modest reduction in their recognition engenders large increases in main ORF translation
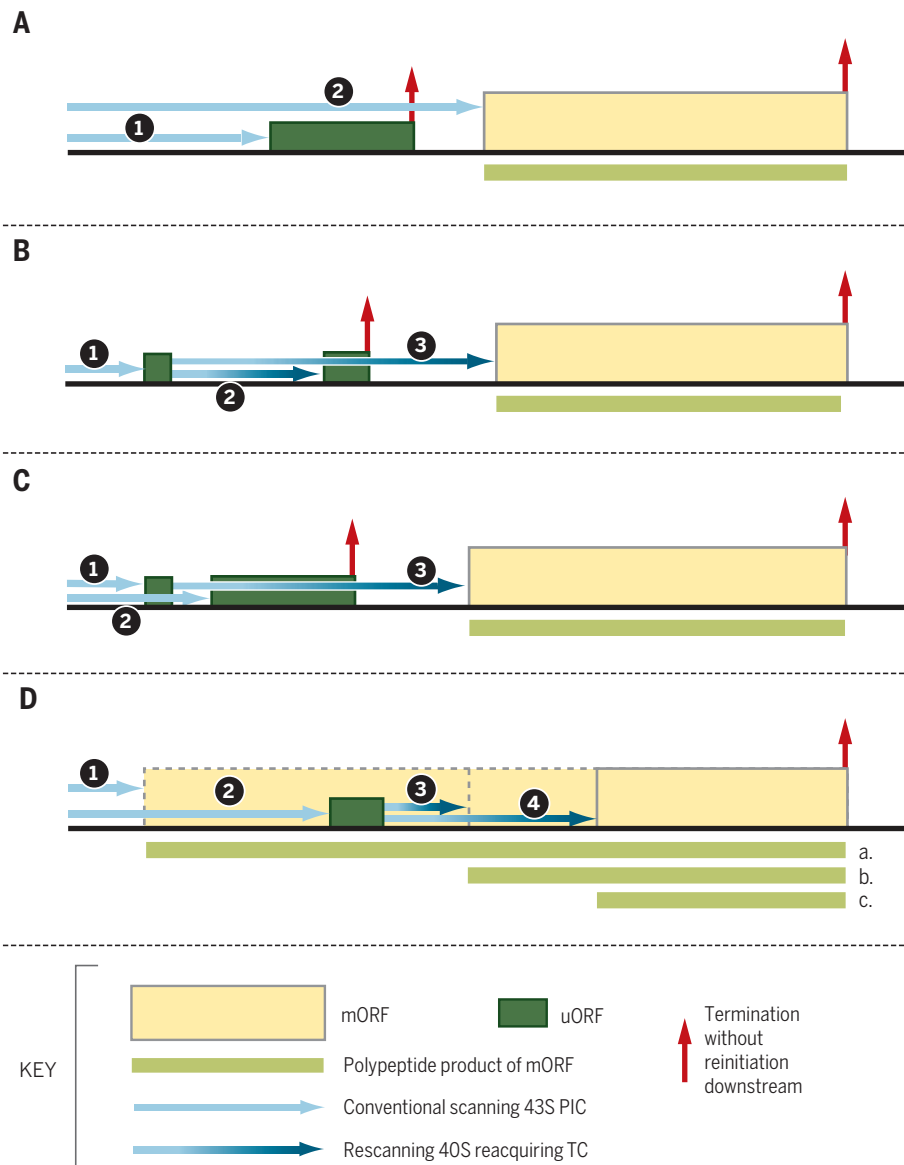

Fig. 3. Different gene architectures conferring translational control by short uORFs. (**A**) 1. Scanning PICs that translate the uORF fail to reinitiate at the mORF, as depicted in Fig. 2. 2. A fraction of scanning PICs leaky-scan the uORF start codon, enhanced by its suboptimal context, and initiate at the mORF instead. Leaky scanning can be inhibited by elevated eIF5 levels, lowering translation of the eIF5 gene itself (*4*); by eIF2(αP), e.g., for *GADD34* (*36*) and *IFRD* (*35*); and by polyamines for *AMD1* (encoding S-adenosylmethionine decarboxylase (SAMDC)) and *AZIN1* (*34*). (**B**) 1. Scanning ribosomes initiate translation of a short uORF whose translation does not preclude reinitiation. 2. Resumed scanning followed by quick reacquisition of TC enables translation of an inhibitory downstream uORF that precludes further reinitiation. 3. Slow reacquisition of TC at reduced TC concentrations evoked by eIF2(αP) allows reinitiation further downstream at the mORF. Examples include *GCN4* (*37*) and *ATF4* (*38, 39*). (**C**) 1. Scanning ribosomes initiate translation of a short uORF permissive for reinitiation. 2. Ribosomes that leaky-scan the first uORF translate a second inhibitory uORF that precludes reinitiation. 3. Ribosomes that translate the first uORF resume scanning and reacquire TC only after bypassing the second uORF, avoiding its inhibitory effect, exemplified by polyamine regulation of SAMDC synthesis in plants (*34*). (**D**) 1. Ribosomes initiate at an upstream start codon in-frame with the mORF and bypass an inhibitory uORF during elongation while producing protein isoform "a" with specific properties. 2. Scanning subunits bypass the in-frame start site, owing to its suboptimal context, and initiate downstream at the uORF. 3. Rescanning followed by quick reacquisition of TC leads to reinitiation at a proximal start codon to produce protein isoform "b". 4. Slow reacquisition of TC allows initiation further downstream producing the shortest isoform, "c," with activities opposite those of "a" and "b." Examples include C/EBP-α and C/EBP-β (*49*).

in stressed cells (*37*). This mechanism enables the rapid, strategic induction of key transcription factors, while the reduced TC levels dampen bulk protein synthesis, for a two-pronged stress response.

The short length of uORF1 is crucial for re-initiation and might facilitate retention of eIF3 during its translation (*37*). Reinitiation after longer uORFs requires additional cis-acting sequences, such as the termination upstream ribosomal binding site (TURBS) element of poly-cistronic calicivirus mRNA that base pairs with 18*S* rRNA sequences of the 40*S* subunit (*41*, *42*), similar to Shine-Dalgarno sequences in bacterial mRNAs and eukaryotic viral IRESs such as in HCV. Some cellular IRESs might also function in this manner (*43*, *44*). The role of eIF3 sub-units in promoting reinitiation appears wide-spread (*45*, *46*). Accessory factors, including ligatin/eIF2D or related proteins MCT-1 and DENR, can promote reinitiation, possibly through an alternative pathway for recovering Met-tRNAi by rescanning PICs (*42*, *47*).

The role of uORFs in regulating reinitiation in response to eIF2(αP) was implicated in learning and memory, neurodegenerative diseases, and cancer. For example, eliminating Gcn2 improved memory in mice owing to decreased eIF2(αP), leading to reduced *ATF4* translation (*48*). Alternative outcomes of leaky scanning versus reinitiation imposed by a uORF in CCAAT/enhancer-binding protein (C/EBP) mRNAs determine the balance of isoforms differing at their N termini, one activating and the other inhibiting transcription, important for mouse liver differentiation and regeneration (Fig. 3D) (*49*). An unusual role for a uORF in facilitating translational repression of *Drosophila msl-2* mRNA in conjunction with 5′UTR binding by sex-lethal (SXL) protein regulates dosage compensation (*50*). There is a growing list of mutations associated with human disease that increase or decrease the influence of uAUGs/uORFs on translation of the main ORF (*28*, *51*).

Other 5′UTR regulatory elements

The 5′ terminal oligopyrimidine (5′TOP) motif plays a role in mammalian target of rapamycin (mTOR)–dependent stimulation of the expression of proteins of the translation machinery to promote cell growth. mTOR complex 1 (mTORC1) activates the La-related protein 1 (LARP1) that binds to the TOP sequence (*52*). Many less-abundant mRNAs lacking 5′TOP exhibit mTOR dependence, encoding mitochondrial and growth/survival-promoting proteins (*53*). Additionally, the m⁶-adenine methylation of 5′UTR sequences seems to have stimulatory effects (*54*).

That uORFs appear to influence translation genome-wide suggests that scanning operates widely in the eukaryotic translatome. However, scanning can be circumvented by specialized elements that enable PICs to enter the 5′UTR internally. mRNAs with a stretch of unstructured nucleotides in the 5′UTR can bypass the requirement for the m⁷G cap and eIF4F, as shown for poly(A) sequences in poxvirus mRNA 5′UTRs (*55*) and CAA nucleotide triplet repeats in the

Ω leader of tobacco mosaic virus mRNAs. Although dispensable for 48*S* assembly per se, eIF4A accelerated the process on a Ω reporter (*56*). eIF4F independence for 48*S* PIC assembly was also observed for mRNAs with synthetic unstructured 5′UTRs, which, like the poly(A) 5′UTRs, still require eIF1, eIF1A, TC, and (in mammals) eIF3 (*8*, *57*). Unstructured nucleotides might bind directly in the mRNA binding cleft of the 40*S* subunit, with ATP hydrolysis by eIF4A enabling subsequent 5′-to-3′ directional scanning. A group of mRNAs in yeast are refractory to widespread translational repression in carbon-starved cells and contain a poly(A) stretch in their 5′UTRs that might recruit eIF4F to the 5′UTR via PABP-eIF4G association, augmenting cap-binding by eIF4F (*58*).

Many viral mRNAs circumvent the scanning process with highly structured IRES elements that interact with the 40*S* subunit or particular eIFs to recruit the PIC to internal sites in the 5′UTR (*59*). These mechanisms persist when cap/eIF4F-dependent initiation is impaired, such as in virus infections where eIF4G is cleaved. Whereas viral IRESs have been extensively characterized biochemically and structurally (*59*), such studies have not been accomplished for potential IRESs in cellular mRNAs (*60*). A genome-wide search yielded a large number of mammalian cellular IRESs (10% of randomly selected 5′UTRs) (*44*), which, if validated for individual mRNAs, would be highly important for understanding gene regulation in humans.

Important progress has been made in elucidating mechanisms by which the 5′UTR regulates translation initiation. This includes molecular and structural understanding of the assembly and recruitment of the PIC to the 5′UTR, scanning, and start codon selection. Acutely lacking is a precise kinetic analysis of the pathway. Single-molecule approaches can be expected to fill this gap and identify intermediate states too transient for detection by ensemble kinetics. Ribosome profiling (*22*) can be adapted to analyze the kinetics and regulation of scanning on all 5′UTRs. Advanced cryo–electron microscopy will continue to yield high-resolution structures of the PIC in different stages of initiation. The new information is bound to aid efforts to discover new drugs to treat diseases whose etiology is associated with dysregulated translation.

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Alan G. Hinnebusch, Ivaylo P. Ivanov, and Nahum Sonenberg

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