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New Concept

How Does a Scanning Ribosomal Particle Move along the 5′-Untranslated Region of Eukaryotic mRNA? Brownian Ratchet Model[†]

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ABSTRACT: A model of the ATP-dependent unidirectional movement of the 43S ribosomal initiation complex (=40S ribosomal subunit + eIF1 + eIF1A + eIF2·GTP·Met-tRNA$_i$ + eIF3) during scanning of the 5′-untranslated region of eukaryotic mRNA is proposed. The model is based on the principles of molecular Brownian ratchet machines and explains several enigmatic data concerning the scanning complex. In this model, the one-dimensional diffusion of the ribosomal initiation complex along the mRNA chain is rectified into the net-unidirectional 5′-to-3′ movement by the Feynman ratchet-and-pawl mechanism. The proposed mechanism is organized by the heterotrimeric protein eIF4F (=eIF4A + eIF4E + eIF4G), attached to the scanning ribosomal particle via eIF3, and the RNA-binding protein eIF4B that is postulated to play the role of the pawl. The energy for the useful work of the ratchet-and-pawl mechanism is supplied from ATP hydrolysis induced by the eIF4A subunit: ATP binding and its hydrolysis alternately change the affinities of eIF4A for eIF4B and for mRNA, resulting in the restriction of backward diffusional sliding of the 43S ribosomal complex along the mRNA chain, while stochastic movements ahead are allowed.

Initiation of translation of eukaryotic mRNA is a complex process consisting of a number of successive distinct stages (for a recent review, see ref *1*). In the first stage, the small (40S) ribosomal subunit binds with proteins eIF1,[1] eIF1A, eIF2, and eIF3 and with initiator Met-tRNA$_i$, resulting in the formation of the 43S ribosomal initiation complex. In the second stage, this complex attaches to 5′ end of the mRNA via another protein, heterotrimeric eIF4F, which forms a bridge between the cap structure of the mRNA and the multisubunit protein eIF3 at the 40S ribosomal subunit. In the third stage, the 43S ribosomal initiation complex moves unidirectionally along the 5′-untranslated region (5′-UTR) of the mRNA in the 5′-to-3′ direction, with accompanying hydrolysis of ATP molecules into ADP and orthophosphate ("ATP-dependent scanning of 5′-UTR"). In the fourth stage, the initiation codon (usually AUG) is recognized, which results in a fixation of the ribosomal complex at the mRNA; now the complex is called the 48S ribosomal initiation complex. In the final (fifth) stage of initiation, the 48S ribosomal complex interacts with eIF5 and eIF5B and subsequently attaches the large (60S) ribosomal subunit; this leads to the release of the initiation factors and the formation of the 80S ribosomal initiation complex, which accommodates the Met-tRNA$_i$ in the peptidyl-tRNA-binding site of the ribosome and becomes ready to start translation of the coding region of mRNA.

The mechanism of ATP-dependent unidirectional movement of the 43S ribosomal complex along the mRNA chain at the region preceding the initiation codon, i.e., along the 5′-UTR, is the most enigmatic stage in the sequence of events described above. The existence of a unidirectional movement mechanism was proposed more than two decades ago by M. Kozak (*2*−*4*) to explain two phenomena: the recognition by an initiating ribosome of the first AUG triplet (starting from the capped 5′ end of the mRNA) as the initiation codon ["translation begins at the 5′ proximal AUG codon" (cited from ref *2*)] and the expenditure of ATP during the process of finding the initiation codon ["ATP is required for the migration of the 40S ribosomal subunits on messenger RNA" (cited from ref *3*)]. The experimental data accumulated since then have never contradicted the scanning model of Kozak, so that the model has become widely recognized. At the same time, the molecular mechanism of the unidirectional movement of the 43S ribosomal complex along the mRNA chain is still unclear, and the discussions are confusing from physical standpoints.

BASIC POSTULATES

By now, the working cycles of a number of biomolecular machines of the conveying or transport type, such as translating ribosomes running on the mRNA chain, RNA polymerases moving along DNA, kinesin molecules stepping on tubulin fibrils, myosin heads walking along actin fibrils, etc., have been described in terms of the Brownian ratchet model (*5*−*13*). It seems evident that, to understand the mechanism of ATP-dependent unidirectional displacements of the scanning ribosomal particle along mRNA as a linear substrate, the following postulates common for all the above-mentioned inertia-free molecular machines should be taken into consideration. (i) Thermal Brownian movement (diffusional displacements) is the

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[1]Abbreviations: eIF, eukaryotic initiation factor (eIF1, eIF1A, eIF2, eIF3, eIF4A, eIF4B, eIF4E, eIF4F, eIF4G, eIF5, and eIF5 are eukaryotic initiation factors 1, 1A, 2, 3, 4A, 4B, 4E, 4F, 4G, 5, and 5B, respectively); Met-tRNA$_i$, initiator methionyl-tRNA; 5′-UTR, 5′-untranslated region.

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source of all spatial motions of macromolecular particles and the mobility of their structural blocks. (ii) Anisotropic environments and structural properties of macromolecules can restrict random motions thus providing anisotropy of thermal movements. (iii) In the case of a linear movement, the structure of a complex between a moving particle and a substrate chain (such as in the complex of the thread/eye-of-needle type) can constrain the three-dimensional random motion into one-dimensional fluctuation, i.e., allows just one-dimensional diffusional wandering along the linear substrate. (iv) The mechanism of the Feynman ratchet (*14*), which allows the displacements in one direction and prevents backward movement ("Maxwell's demon" with energy feeding), must exist to provide the net unidirectionality of the diffusional movement of the particle along the linear substrate. (v) As a rule, it is ATP that serves the molecular Feynman ratchet-and-pawl mechanism for energy feed: alternating ATP binding and hydrolysis cause conformational changes of an "engine" module within the moving particle, and this results in alternating changes in the affinity of the moving particle for the linear substrate. Usually, ATP binding induces a closed (locked) conformation of the "engine protein" with high affinity, whereas ATP hydrolysis leads to an open (unlocked, relaxed) conformation with a lower affinity for a linear substrate.

FACTUAL PREREQUISITES

It is known that the heterotrimer protein eIF4F consisting of subunits eIF4E (α), eIF4A (*β*), and eIF4G (*γ*) can be physically connected to the 43S ribosomal complex because of the interaction of the eIF4G subunit with the large multimeric protein eIF3, which is firmly associated with the ribosomal particle at all stages of the initiation process (*1*). Thus, the moving 43S ribosomal complex can include eIF4F, with or without its cap-recognizing subunit eIF4E. Indeed, experimental data suggest the presence of eIF4F or the eIF4G·eIF4A heterodimer in the scanning complex (*15*). The presence of eIF4F or the eIF4G·eIF4A complex must be principally important for unidirectional movement of the scanning ribosomal complex, because the eIF4A subunit is the only component that can bind ATP and catalyze its hydrolysis with the corresponding conformational changes. There are all grounds to assert that, when the two-domain protein eIF4A binds ATP, it acquires a closed (locked) conformation: its domains become drawn together (*16*, *17*), and the protein gains a strong affinity for a single-stranded RNA (*18*). It is the affinity of eIF4A with ATP for a single-stranded RNA that seems to be responsible for its limited ability to unwind the secondary structure of RNA, possibly via a steric mechanism (*19*), so that the protein may be qualified as an ATP-dependent nonprocessive RNA helicase. On the other hand, the bound single-stranded RNA induces ATPase activity of eIF4A, thus allowing one to consider this protein as an RNA-dependent ATPase (for a review, see ref *20*.). The hydrolysis of the eIF4A-bound ATP results in the unlocking of the two domains of the protein. The unlocked protein loses its strong affinity for RNA, leading to the dissociation of the protein from RNA. Combined, these data support the idea that the eIF4A subunit is a possible engine of the moving 43S ribosomal initiation complex: the protein uses the chemical potential of ATP as "fuel" for the Feynman ratchet, alternately changing its conformation and, correspondingly, its affinity for RNA as a transport substrate. However, this does not explain yet how the energy-dependent locking and unlocking of the protein and its alternating affinity changes for RNA are transformed into the unidirectional movement of the initiation complex. The alternate binding of the protein subunit to the RNA chain and the release from it cannot lead to anything except wandering. "A *directed* cycle, and hence a *directed* motion is possible only when the number of states exceeds two (two states only allow oscillating back and forth)" (cited from ref *21*).

Two additional observations favor a proposal for a plausible model for transmission and mover mechanisms of the scanning 43S ribosomal complex as a molecular machine. First, it has been shown that the unidirectional ATP-dependent movement of the initiation complex involves an additional protein: this is eIF4B, which is not a permanent component of the scanning complex, but must be present in the milieu for effective scanning (*1*, *20*, *22*, *23*). The eIF4B is an ATP-independent RNA-binding protein. Although most aspects of eIF4B functioning are not clear yet and further experimentations, especially concerning its kinetic parameters, are required, a preliminary description of some properties of the protein can be done (for a review, see ref *20*). With respect to its interaction with RNA, eIF4B seems to exhibit rather slow rates of association with RNA and dissociation. However, eIF4B can interact with the closed (locked) form of eIF4A in the presence of ATP. The interaction of eIF4B with eIF4A strongly stimulates the RNA binding activity of both proteins and the ATP hydrolyzing activity of eIF4A, as well as the rate of subsequent dissociation of eIF4A in the open form (with bound ADP) both from RNA and from eIF4B. Moreover, the interaction of eIF4A with eIF4G, which takes place in the trimeric factor eIF4F, enhances these effects: eIF4A complexed with eIF4G in the presence of eIF4B (or its homologue eIF4H) manifests a maximal affinity for RNA prior to ATP hydrolysis, a maximal rate of ATP hydrolysis, and a maximal rate of the release from RNA after ATP hydrolysis (*20*, *23*−*26*).

Second, on the basis of the cryo-electron microscopy study, the localization of eIF4F (more precisely, its large subunit eIF4G) on the initiation ribosomal complex was modeled (*27*). eIF4G, as well eIF3, was placed at the rear (facing 5′ end of mRNA chain) of the moving ribosomal particle. Hence, according to the model, during movement of the 43S ribosomal initiation complex along the mRNA chain, the eIF4A subunit attached to eIF4G trails after the ribosomal particle and in no way forces the road ahead.

The following conclusions can be drawn from the discussion above. (i) As the eIF4A module is located at the rear of the moving 43S ribosomal complex, where unwinding of the secondary structure of RNA is pointless, it is the ATP-dependent RNA binding function of the protein, rather than its weak RNA unwinding function, that should be used by the movement mechanism. (ii) Binding of ATP by the eIF4A module leads to attachment to the mRNA chain and at the same time to the recruitment of the free RNA binding protein eIF4B, and the two proteins together are capable of firmly anchoring the 43S complex at a given position of the substrate RNA chain. (iii) The hydrolysis of ATP on the eIF4A module results in the release of the module from the RNA and weakens the interaction between eIF4A and eIF4B, and thus, the entire 43S complex becomes unanchored. (iv) If after the ATP hydrolysis and dissociation of the eIF4A·eIF4B complex the eIF4B continues to be bound to the RNA for some time because of its low dissociation rate, it can play the role of the pawl that restricts a backward diffusional movement of the 43S ribosomal complex, while a forward diffusional shift along the substrate mRNA chain is allowed.

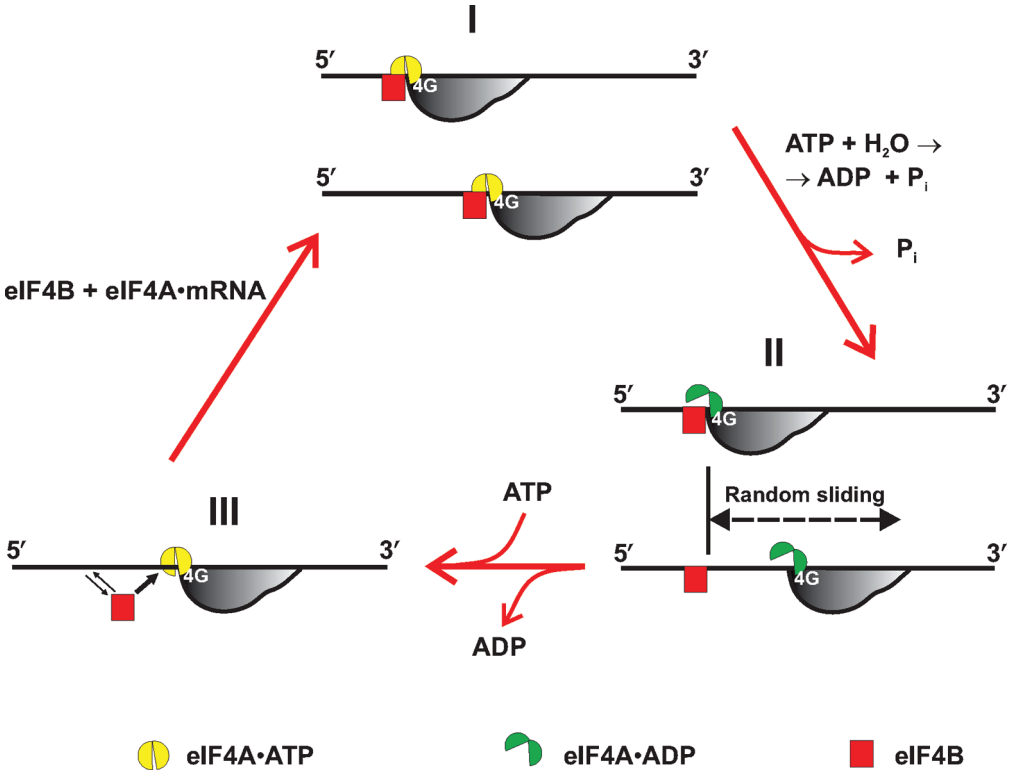

FIGURE 1: Scheme of the working cycle of a scanning ribosomal complex. The 40S ribosomal particle is shown in the orientation where the head is facing the viewer with the beak directed to the right, and the mRNA-conducting groove is on top; in this orientation, the particle is symbolized by the upside-down "mouse" contour. eIF3 and eIF4F are localized at the rear (trailing side) of the particle, and the site of eIF4G subunit of eIF4F is designated as 4G. The eIF4A subunit of eIF4F is symbolized by two hemispheres, either locked together (eIF4A·ATP, yellow) or somewhat drawn apart (eIF4A·ADP, green), and eIF4B by a red square. State I (the mRNA-fixed complex) is the starting point of the cycle when the 40S ribosomal particle is complexed with eIF4A·ATP via eIF4G at the trailing side of the particle, and eIF4B is bound both to eIF4A·ATP and mRNA. The entire ribosomal complex is anchored at the mRNA chain by the eIF4B·eIF4A·ATP complex. The RNA-induced hydrolysis of eIF4A-bound ATP leads to state II (the released complex) in which eIF4A·ADP has lost its interactions with mRNA and eIF4B, resulting in unanchoring of the ribosomal complex from the mRNA chain. In this state, the complex can diffusionally slide along mRNA chain, but the mRNA-attached eIF4B prevents backward diffusional movements. State III (the stand-by complex) results from the binding of ATP to eIF4A (ADP/ATP replacement), which restores the affinity of eIF4A for mRNA and thus fixes the complex at a new, forward-shifted position. The complex again includes eIF4A·ATP and now will attract eIF4B, after its slow dissociation from the previous position on mRNA ("the weak to strong binding state transition") or from the pool of free initiation factors; the ribosomal complex returns to the original state I. Thus, each cycle results in one act of a net unidirectional diffusional shift along the 5′-UTR of a eukaryotic mRNA toward the 3′ end.

BROWNIAN RATCHET MODEL OF UNIDIRECTIONAL MOVEMENT OF THE SCANNING RIBOSOMAL COMPLEX

In Figure 1, the model of a plausible mechanism for the unidirectional movement of the scanning ribosomal particle (the 43S initiation complex) based on the general principles of molecular machines is presented. The position of the initiator 43S ribosomal complex anchored on the mRNA chain by the eIF4A subunit in the ATP-induced locked conformation is taken to be the starting state (state I) of the working cycle. The RNA binding protein eIF4B interacts with the eIF4A subunit and thus contributes to the fixation of the 43S complex on the mRNA.

Stroke 1. Hydrolysis of eIF4A-bound ATP is induced by the RNA and enhanced by the interaction with eIF4B, leading to a conformational change (unlocking) of the eIF4A subunit of eIF4F and loss of its affinities for the mRNA chain and for the mRNA-bound eIF4B. As a result, the 43S ribosomal complex becomes free for diffusional sliding along the mRNA chain (state II). However, the temporary presence of the slowly dissociating protein eIF4B on mRNA just behind the ribosomal particle prevents its shift backward (toward the 5′ end of mRNA) and allows only a forward shift (toward the 3′ end). [Naturally, when dissociation of eIF4B from mRNA occurs before the next stage, the occasional backward shifts are also allowed. Nevertheless, this keeps the net unidirectional character of the 43S complex movement and should not significantly affect the linearity of the plot of scanning time versus the 5′-UTR length dependence (see ref *31*).]

Stroke 2. Binding of ATP to the eIF4A subunit (exchange of ADP for ATP) results in locking of the protein domains, resumption of the affinity for RNA, and, hence, fixation of the entire 43S ribosomal complex at a new, 3′-advanced position on mRNA chain (state III). Thus, a certain shift ahead (toward the 3′ end) becomes completed and fixed. It should be emphasized that this diffusional "step" (transition from state II to state III) is a stochastic net-directed displacement rather than a measured step of a definite length.

Stroke 3. Protein eIF4B, being in a slowly attained equilibrium between RNA-bound and free states, switches to a stronger binding state by interaction with the RNA-bound eIF4A subunit in the ATP-induced locked conformation (reversion to state I) ["the weak to strong binding state transition" (see ref *6*)].

Hence, according to the proposed model, the working cycle of the molecular machine under consideration includes three successive conformational states of the initiation 43S ribosomal complex. The result of the conformational transitions described is the performance of one act of stochastic movement of the particle

along the mRNA chain in the 3′ direction. As a whole, the cycle can be considered as a molecular Feynman ratchet wheel where the protein eIF4B plays the role of a pawl, and the protein eIF4A is an engine that uses ATP as fuel to alternately lock and release the pawl.

DISCUSSION AND CONCLUSION

In accordance with Kozak's original proposal, scanning during translation initiation is the process of searching for the initiation codon by a small ribosomal particle via its unidirectional movement along the mRNA chain from the 5′ end toward the 3′ end of the mRNA. It is clear that the unidirectionality of the movement in itself requires energy, independent of the problem of secondary structure unwinding. An ATP-independent unidirectional movement along any polyribonucleotide sequence, including unstructured mRNA regions, would be in violation of the second law of thermodynamics. The reported cases of correct finding of initiation codons without ATP or ATP-hydrolyzing initiation factors should be interpreted as the result of a random (nondirected) diffusional "wandering" of mRNA-bound 40S subunits along unstructured or weakly structured polyribonucleotide chain regions (*28*−*30*).

At the same time, the ATP-dependent unidirectional movement of the ribosomal complex along the 5′-UTR of mRNA will usually encounter obstacles in the form of secondary and tertiary structures of different stabilities. The solution to this problem requires additional mechanisms and a source of additional energy for overcoming the kinetic barriers. The problem may be solved by the involvement of various ATP-dependent helicases. Among them is the eIF4A in its free form (i.e., the eIF4A that is not a subunit of eIF4F or the eIF4G·eIF4A complex), a comparatively slow and weakly efficient nonprocessive helicase with poorly identified biological functions (*20*). The free eIF4A is the most abundant initiation factor in eukaryotic cells. The possibility that the nonprocessive helicase activity of the free eIF4A can maintain the half-melted state of RNA by alternating ATP-dependent binding to RNA and subsequent ATPase-induced dissociation from it cannot be excluded. However, as recently shown using atomic force microscopy, eIF4A by itself is impotent in unwinding stem−loop structures of RNA (*19*). In any case, it should be mentioned again that the participation of free RNA helicases in the process of scanning is not directly relevant to the problem of unidirectionality of movement during scanning.

An interesting possibility might be the presence of an RNA helicase attached to the ribosomal particle at the entrance of the mRNA channel of the small ribosomal subunit. In particular, because of the U-turn of mRNA around the neck of the 40S ribosomal subunit, it is spatially possible that eIF4A is found in front of the scanning complex, while the eIF4A-binding domain of eIF4G is near the mRNA at the 5′ side (*26*). In such a case, eIF4B, like eIF4H (*26*), could contact mRNA behind eIF4A, but in front of the 40S subunit. Evidently, this situation does not contradict the scanning model proposed: the model requires eIF4B to be positioned behind the eIF4A subunit of eIF4F, whereas the position of eIF4F on the ribosomal subunit is not critical.

According to the proposed model, the eIF4B protein plays a principal role in the unidirectional movement of the ribosomal complex as the pawl in the Brownian ratchet mechanism (Figure 1). Therefore, eIF4B is not merely stimulatory for eIF4A helicase, as commonly accepted, but can be strictly required for the working cycle of the ratchet mechanism. It is possible that a smaller homologous protein, eIF4H, can functionally substitute for eIF4B to some extent (see ref *26*). Hence, the prediction made from the model is that the omission of eIF4B and eIF4H from the experimental system of translation initiation must fully stop the movement of the scanning ribosomal complex.

In summary, the scanning 43S ribosomal initiation complex, associated with eIF4F and accompanied by free eIF4B, can be considered as an isothermal molecular machine of the transport or conveying type. The machine moves along the mRNA chain due to rectified thermal fluctuations. The construction of the machine constrains the three-dimensional random motion into one-dimensional diffusion. The net unidirectionality of the linear movements, with occasional backward motions, is achieved at the expense of the free energy of the ATP hydrolysis reaction. This is realized in the restriction of diffusional backward shifts by the combination of the 43S ribosomal complex-bound eIF4A and the free eIF4B, which alternately change their affinities for each other and for mRNA (energized "Maxwell's demon").

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REFERENCES

1. Pestova, T. V., Lorsh, J. R., and Hellen, C. U. T. (2007) The mechanism of translation initiation in eukaryotes. In Translational Control in Biology and Medicine (Mathews, M. B., Sonenberg, N., and Hershey, J. W. B., Eds.) pp 87−128, Cold Spring Harbor Laboratory Press, Plainview, NY.
2. Kozak, M. (1978) How do eucaryotic ribosomes select initiation regions in messenger RNA? *Cell 15*, 1109–1123.
3. Kozak, M. (1980) Role of ATP in binding and migration of 40S ribosomal subunits. *Cell 22*, 459–467.
4. Kozak, M. (1989) The scanning model for translation: An update. *J. Cell Biol. 108*, 229–241.
5. Spirin, A. S. (1985) Ribosomal translocation: Facts and models. *Prog. Nucleic Acid Res. Mol. Biol. 32*, 75–114.
6. Vale, R. D., and Oosawa, F. (1990) Protein motors and Maxwell's demons: Does mechanochemical transduction involve a thermal ratchet? *Adv. Biophys. 26*, 97–134.
7. Cordova, N. J., Ermentrout, B., and Oster, G. F. (1992) Dynamics of single-motor molecules: The thermal ratchet model. *Proc. Natl. Acad. Sci. U.S.A. 89*, 339–343.
8. Gelles, J., and Landick, R. (1998) RNA polymerase as a molecular motor. *Cell 93*, 13–16.
9. Spirin, A. S. (2002) Ribosome as a molecular machine. *FEBS Lett. 514*, 2–10.
10. Nishiyama, M., Higuchi, H., Ishii, Y., Taniguchi, Y., and Yanagida, T. (2003) Single molecule processes on the stepwise movement of ATP-driven molecular motors. *BioSystems 71*, 145–156.
11. Ait-Haddou, R., and Herzog, W. (2003) Brownian ratchet models of molecular motors. *Cell Biochem. Biophys. 38*, 191–214.
12. Yanagida, T., Ueda, M., Murata, T., Esaki, S., and Ishii, Y. (2007) Brownian motion, fluctuation and life. *BioSystems 88*, 228–242.
13. Spirin, A. S. (2009) The ribosome as a conveying thermal ratchet machine. *J. Biol. Chem. 284*, 21103–21119.
14. Feynman, R., Leighton, R., and Sands, M. (1963) The Feynman Lectures on Physics , Addison-Wesley, Reading, MA.
15. Pöyry, T. A., Kaminski, A., and Jackson, R. J. (2004) What determines whether mammalian ribosomes resume scanning after translation of a short upstream open reading frame? *Genes Dev. 18*, 62–75.
16. Lorsch, J. R., and Herschlag, D. (1998) The DEAD box protein eIF4A. 2. A cycle of nucleotide and RNA-dependent conformational changes. *Biochemistry 37*, 2194–2206.
17. Caruthers, J. M., Johnson, E. R., and McKay, D. B. (2000) Crystal structure of yeast initiation factor 4A, a DEAD-box RNA helicase. *Proc. Natl. Acad. Sci. U.S.A. 97*, 13080–13085.
18. Lorsch, J. R., and Herschlag, D. (1998) The DEAD box protein eIF4A. 1. A minimal kinetic and thermodynamic framework

reveals coupled binding of RNA and nucleotide. *Biochemistry 37*, 2180–2193.
19. Marsden, S., Nardelli, M., Linder, P., and McCarthy, J. E. G. (2006) Unwinding single RNA molecules using helicases involved in eukaryotic translation initiation. *J. Mol. Biol. 361*, 327–335.
20. Rogers, G. W., Komar, A. A., and Merrick, W. C. (2002) eIF4A: The godfather of the DEAD box helicases. *Prog. Nucleic Acid Res. Mol. Biol. 72*, 307–331.
21. Finkelstein, A. V., and Ptitsyn, O. B. (2002) Protein Physics, Academic Press, London.
22. Pestova, T. V., and Kolupaeva, V. G. (2002) The roles of individual eukaryotic translation initiation factors in ribosomal scanning and initiation codon selection. *Genes Dev. 16*, 2906–2922.
23. Marintchev, A., and Wagner, G. (2004) Translation initiation: Structures, mechanisms and evolution. *Q. Rev. Biophys. 37*, 197–284.
24. Oberer, M., Marintchev, A., and Wagner, G. (2005) Structural basis for the enhancement of eIF4A helicase activity by eIF4G. *Genes Dev. 19*, 2212–2223.
25. Schütz, P., Bumann, M., Oberholzer, A. E., Bieniossek, C., Trachsel, H., Altmann, M., and Baumann, U. (2008) Crystal structure of the yeast eIF4A-eIF4G complex: An RNA-helicase controlled by protein-protein interactions. *Proc. Natl. Acad. Sci. U.S.A. 105*, 9564–9569.
26. Marintchev, A., Edmonds, K., Marintcheva, B., Hendrickson, E., Oberer, M., Suzuki, C., Herdy, B., Sonenberg, N., and Wagner, G. (2009) Topology and regulation of the human eIF4A/4G/4H helicase complex in translation initiation. *Cell 136*, 447–460.
27. Siridechadilok, B., Fraser, C. S., Hall, R. J., Doudna, J. A., and Nogales, E. (2005) Structural roles for human translation factor eIF3 in initiation of protein synthesis. *Science 310*, 1513–1515.
28. Sarabhai, A., and Brenner, S. (1967) A mutant which reinitiates the polypeptide chain after chain termination. *J. Mol. Biol. 27*, 145–162.
29. Adhin, M. R., and van Duin, J. (1990) Scanning model for translational reinitiation in eubacteria. *J. Mol. Biol. 213*, 811–818.
30. Shirokikh, N. E., and Spirin, A. S. (2008) Poly(A) leader of eukaryotic mRNA bypasses the dependence of translation on initiation factors. *Proc. Natl. Acad. Sci. U.S.A. 105*, 10738–10743.
31. Berthelot, K., Muldoon, M., Rajkowitsch, L., Hughes, J., and McCarthy, J. E. G. (2004) Dynamics and processivity of 40S ribosome scanning on mRNA in yeast. *Mol. Microbiol. 51*, 987–1001.