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Review

A new framework for understanding IRES-mediated translation

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ABSTRACT

Studies over the past 5 or so years have indicated that the traditional clustering of mechanisms for translation initiation in eukaryotes into cap-dependent and cap-independent (or IRES-mediated) is far too narrow. From individual studies of a number of mRNAs encoding proteins that are regulatory in nature (i.e. likely to be needed in small amounts such as transcription factors, protein kinases, etc.), it is now evident that mRNAs exist that blur these boundaries. This review seeks to set the basic ground rules for the analysis of different initiation pathways that are associated with these new mRNAs as well as related to the more traditional mechanisms, especially the cap-dependent translational process that is the major route of initiation of mRNAs for housekeeping proteins and thus, the bulk of protein synthesis in most cells. It will become apparent that a mixture of descriptions is likely to become the norm in the near future (i.e. m^7G-assisted internal initiation).

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1. Introduction

The purpose of this review is to pose some questions, and perhaps provide a few answers, as relates to the process of translation initiation and the regulation of this process, termed translation control. To do this requires that one have a feel for the total picture of translation so that the unique bits and pieces can be fit into particular quarters. In contrast to bacterial systems where transcriptional control is predominant, in eukaryotic systems roughly 30% of the mass of cellular protein made is subject to translational control. A part of this reflects the unique difference between eukaryotes and prokaryotes which is that in eukaryotes the mRNA emerges from the nucleus as an mRNP (Glisovic et al., 2008) that is approximately half RNA/half protein while in bacterial systems the mRNA is essentially available as a naked transcript in the same compartment as the translating ribosome where often the mRNA is in bound to ribosomes before transcription has been completed. Secondly, regulation of gene expression at the level of translation not only offers an additional

Abbreviations: eIF, eukaryotic initiation factor; UTR, untranslated region; IRES, internal ribosome entry site; ORF, open reading frame; EMCV, encephalomyocarditis virus; HCV, hepatitis C virus; HA, heme agglutinin; PABP, poly(A)-binding protein; ITAF, IRES trans-acting factor.

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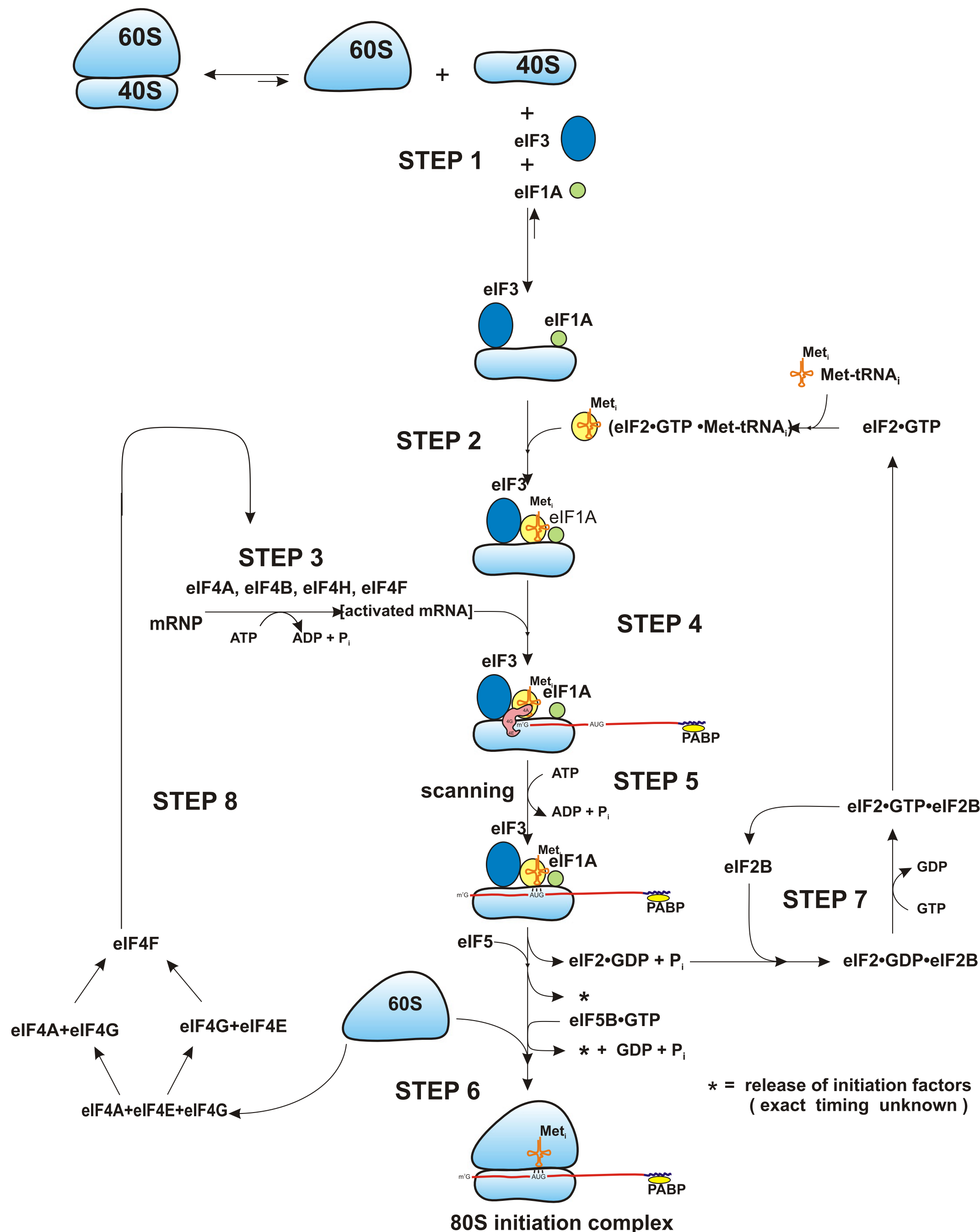

Fig. 1. The "traditional" 80S pathway.Pictured above is an 80S pathway that has been supported by studies examining the requirements for the formation of different intermediates of the pathway and some kinetic analyses. Limitations on the accuracy of this pathway are discussed in the text. A key feature to note is that steps 7 and 8 are the primary sites of global regulation of protein synthesis. In theory, regulation at step 7 should reduce expression of all mRNAs equally while regulation at step 8 should drive mRNA competition such that less efficient mRNAs are affected much more than highly competitive mRNAs. This figure is from Merrick, 2010 and used with permission from the Journal of Biological Chemistry, American Society for Biochemistry and Molecular Biology.

point for fine tuned control, but also a more rapid response system (i.e. conversion of an inactive mRNA to an active mRNA would not require transcription, processing or transport).

2. Cap-dependent translation

As the result of numerous studies in the 1970s and 1980s, a loose description of cap-dependent translation was formulated (Merrick, 1992). Although based upon a few test mRNAs, the general principles derived seemed to apply to most cellular mRNAs. In its simplest, the steps involved were:

1. Binding of eIF3 to 40S subunits to block joining with the 60S subunit and thus provide a pool of small ribosomal subunits on which to build an initiation complex.
2. Binding of the ternary complex of eIF2•GTP•Met-tRNA$_i$ to the 40S subunit (to form a 43S complex).
3. Binding of eIF4F (and eIF4A and eIF4B) to mRNPs for ATP-dependent activation (generally the removal of proteins and/or secondary structure from the 5′ end of the mRNA).
4. Binding of the activated mRNA to 43S subunits.
5. Scanning of the mRNA to identify the initiating AUG codon.
6. Hydrolysis of the GTP in the ternary complex (and possible release of factors) and eIF5B-directed subunit joining (with GTP hydrolysis).

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