# Metadata of the chapter that will be visualized online

| | | |
|---|---|---|
| Chapter Title | Eukaryotic Translation Initiation Factor Interactions | |
| Copyright Year | 2012 | |
| Copyright Holder | Springer Science+Business Media, LLC | |
| Corresponding Author | Family Name | **You** |
| | Particle | |
| | Given Name | **Tao** |
| | Suffix | |
| | Division/Department | Computational Biology, Innovative Medicines |
| | Organization/University | AstraZeneca |
| | Street | Mereside, Alderley Park |
| | City | Macclesfield |
| | State | Cheshire |
| | Postcode | SK10 4TG |
| | Country | UK |
| | Phone | +44 (0)1625 514733 |
| | Email | youtao80@gmail.com |
| Author | Family Name | **Coghill** |
| | Particle | |
| | Given Name | **George M.** |
| | Suffix | |
| | Division/Department | Institute for Complex System & Mathematical Biology |
| | Organization/University | University of Aberdeen |
| | Street | Foresterhill |
| | City | Aberdeen |
| | Postcode | AB25 2ZD |
| | Country | UK |
| | Phone | +44 (0)1224 273829 |
| | Email | g.coghill@abdn.ac.uk |
| Author | Family Name | **Brown** |
| | Particle | |
| | Given Name | **Alistair J.P.** |
| | Suffix | |
| | Division/Department | Microbiology |
| | Organization/University | Institute of Medical Sciences, University of Aberdeen |

| | |
|---|---|
| Street | Foresterhill |
| City | Aberdeen |
| Postcode | AB25 2ZD |
| Country | UK |
| Phone | +44 (0)1224 555883 |
| Fax | +44 (0)1224 555844 |
| Email | al.brown@abdn.ac.uk |

E

# Eukaryotic Translation Initiation Factor Interactions

Tao You[1], George M. Coghill[2] and Alistair J.P. Brown[3]
[1]Computational Biology, Innovative Medicines, AstraZeneca, Macclesfield, Cheshire, UK
[2]Institute for Complex System & Mathematical Biology, University of Aberdeen, Aberdeen, UK
[3]Microbiology, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

## Synonyms

Eukaryotic translation initiation pathway

## Definition

Eukaryotic translation initiation is the process that allows a ribosome to assemble at the start codon on a messenger RNA. A set of proteins known as eukaryotic translation initiation factors (► eIFs) orchestrates this process along with the two ribosomal subunits and initiator tRNA. Some of the events in this process happen in a specific temporal order. The cooperativity among protein interactions gives rise to some defined preinitiation complexes.

## Characteristics

### Eukaryotic Translation Initiation Process

In eukaryotic cells, eIF2 preferentially binds GDP. The guanine nucleotide exchange factor eIF2B replaces this GDP to GTP, but only on the unphosphorylated form of eIF2 (Fig. 1a: $v_1$), so as to comprise the ► ternary complex (i.e., TC, comprising eIF2, GTP, and initiator methionyl-tRNA, Met-tRNA$_i$). This ternary complex is essential for translation initiation (Fig. 1a: $v_2$). The interaction between eIF1A and the ► 40S ribosomal subunit promotes the dissociation of a ► ribosome and ensures that the 40S ribosomal subunit is open to receive other eIFs. Subsequently, eIF1, eIF3, eIF5, and ternary complex are recruited to the 40S ribosomal subunit thereby generating the ► 43S preinitiation complex, in which the initiator tRNA Met-tRNA$_i$ is held close to the ribosome's P site (Sonenberg and Hinnebusch 2009). This may happen via binding of the individual factors to the 40S ribosomal subunit in separate steps. On the other hand, these factors may interact through cooperative binding. There is evidence to suggest that these factors load onto the 40S ribosomal subunit in the form of a multifactor complex (Fig. 1a: $v_3$, $v_4$, Asano et al. 2000). Also various partial complexes have been isolated. Therefore, the multifactor complex may form via different routes, as shown in Fig. 1b (You et al. 2010).

eIF4E interacts with the 5′ cap structure of an mRNA (beginning of an mRNA), and poly-A binding protein (PABP) binds the poly-A structure at the 3′ end (mRNA's end), as depicted in Fig. 1c. eIF4G circularizes the mRNA by binding both eIF4E and PABP. eIF4G also recruits the mRNA helicase eIF4A and its

W. Dubitzky, O. Wolkenhauer, K. Cho & H. Yokota (eds.), *Encyclopedia of Systems Biology*,
DOI 10.1007/978-1-4419-9863-7, 

activating partner eIF4B, which removes mRNA secondary structures that might impede the movement of the ▶ ribosome during scanning (below). This entire complex is known as eIF4F (Fig. 1c).

The 43S preinitiation complex loads onto the 5′ end of an mRNA via multiple interactions between eIF3/eIF5 and eIF4E/eIF4B complexes (Fig. 1a: $v_5$). Subsequently, the complex moves down the mRNA in a 3′ direction, seeking the 5′ proximal start codon, in a process known as scanning (Fig. 1a: $v_6$). eIF5 catalyzes the hydrolysis of GTP bound to eIF2, which is in equilibrium with GDP plus phosphate (Fig. 1a: $v_7$). Base pairing between the anticodon loop of the initiator tRNA Met-tRNA$_i$ and the start codon leads to a change in the conformation of the 43S preinitiation complex. This triggers release of eIF1 in a mechanism involving eIF1A and eIF5 (Fig. 1a: $v_8$, Lorsch and Dever 2010). This leads to release of the phosphate, GDP, eIF2, and eIF5, and commits the 40S ribosomal subunit in an immobilized closed conformation over the start codon (Fig. 1a: $v_9$, Sonenberg and Hinnebusch 2009).

Next, eIF5B·GTP is recruited to the 40S ribosomal subunit (Fig. 1a: $v_{10}$). The ▶ 60S ribosomal subunit joins the complex after the hydrolysis of this eIF5B-bound GTP (Fig. 1a: $v_{11}$) and the release of the phosphate, eIF1A and eIF5B (Fig. 1a: $v_{12}$, $v_{13}$). Upon completion of the translation initiation process, a ribosome is poised at the start codon ready for translation elongation (Sonenberg and Hinnebusch 2009).

## Multifactor Complex

As described above, assembly of the 43S preinitiation complex relies on a multifactor complex. The cooperative binding between the individual factors that comprise multifactor complex means a partial complex has higher affinity with the binding partners compared with the individual components of the partial complex. This stimulation favors the formation of a complete multifactor complex, and hence ensures the proper assembly of a functioning 43S preinitiation complex. The multifactor complex contains equimolecular amounts of the individual factors. However, these eIFs are not equimolar in vivo (von der Haar and McCarthy 2002). The optimal operation of the translation initiation apparatus relies on the complex interactions among the eIFs, and overexpression of a specific eIF does not necessarily lead to higher protein synthesis activities. For instance, overexpression of eIF5 sequesters eIF2·GDP in a nonproductive eIF5·eIF2·GDP complex, thereby reducing protein synthesis (Singh et al. 2006; You et al. 2010).

## eIFs Control Protein Synthesis

According to ▶ metabolic control theory, control over a multistep process is distributed among the enzymes that catalyze each step, and there is no specific rate-limiting step. Hence, control over protein synthesis is not exerted upon the activity of only one eIF. Instead, such control is distributed among different factors. A further complication is that the topology of the network that gives rise to the multifactor complex is not linear. To characterize the control of protein synthesis by a specific eIF in a small perturbation regime, a local flux control coefficient is introduced:

$$C^J_{\mathrm{eIF}} = \frac{\mathrm{eIF}}{J} \cdot \frac{\partial J}{\partial \mathrm{eIF}}, \qquad (1)$$

where $J$ denotes the protein synthesis rate. This control coefficient is a normalized value, and it illustrates how sensitive the protein synthesis is to a small perturbation around a particular eIF activity, while keeping the activity of other eIFs constant.

Experimental work demonstrates that some of the eIFs exert a biphasic mode of control. $C^J_{\mathrm{eIF}}$ is small at small reduction in eIF, indicating that protein synthesis is relatively robust against small decrease in eIF activities. Below a certain threshold, $C^J_{\mathrm{eIF}}$ assumes a higher value. This means that protein synthesis becomes sensitive to the activity of an eIF once this eIF is reduced below certain value (Sangthong et al. 2007).

Computational modeling has provided additional insights. Significantly, modeling predicts that eIF2 has the highest impact on protein synthesis rate, while eIF1 is among those factors with the least impact on protein synthesis rate (Dimelow and Wilkinson 2009; You et al. 2010). eIF2 binds initiator tRNA Met-tRNA$_i$ as well as the GTP whose hydrolysis is central to start codon recognition. Therefore, reducing eIF2 activity would directly affect the levels of the multifactor complex and consequently the 43S preinitiation complex. Therefore, sufficient levels of eIF2 expression are important for efficient translation.

On the other hand, eIF1 has a critical role in start codon recognition. Evolution might have led to the maintenance of high eIF1 activities in vivo to ensure that mRNA translation is not impeded at the initiation step by this factor.

## Modes of Control in Translation Initiation

4E-BP (eIF4E binding protein) competitively binds eIF4E, and inhibits its interaction with eIF4G (Fig. 1c). In mammals the activity of 4E-BP is negatively regulated by mTORC1 (mammalian target of rapamycin complex 1). When nutrients are limiting, mTORC1 activity is lowered. This increases the activity of 4E-BP and eventually reduces protein synthesis via inhibition of eIF4E (Sonenberg and Hinnebusch 2009).

In addition, the activities of eIF2 and eIF2B are negatively regulated in response to stress conditions (see ▶ Translational Control of GCN4). A reduction in eIF2 activity leads to global translational arrest, while some specific mRNA species gain higher translation activity in mechanism involving upstream open reading frames.

## Cross-References

- ▶ 40S Ribosomal Subunit
- ▶ 43S Preinitiation Complex
- ▶ 60S Ribosomal Subunit
- ▶ eIF
- ▶ Translational Control of GCN4

## References

Asano K, Clayton J, Shalev A, Hinnebusch AG (2000) A multifactor complex of eukaryotic initiation factors, eIF1, eIF2, eIF3, eIF5, and initiator tRNA(Met) is an important translation initiation intermediate in vivo. Genes Dev 14(19):2534–2546

Dimelow RJ, Wilkinson SJ (2009) Control of translation initiation: a model-based analysis from limited experimental data. J R Soc Interface 6(30):51–61

Lorsch JR, Dever TE (2010) Molecular view of 43S complex formation and start site selection in eukaryotic translation initiation. J Biol Chem 285(28):21203–21207

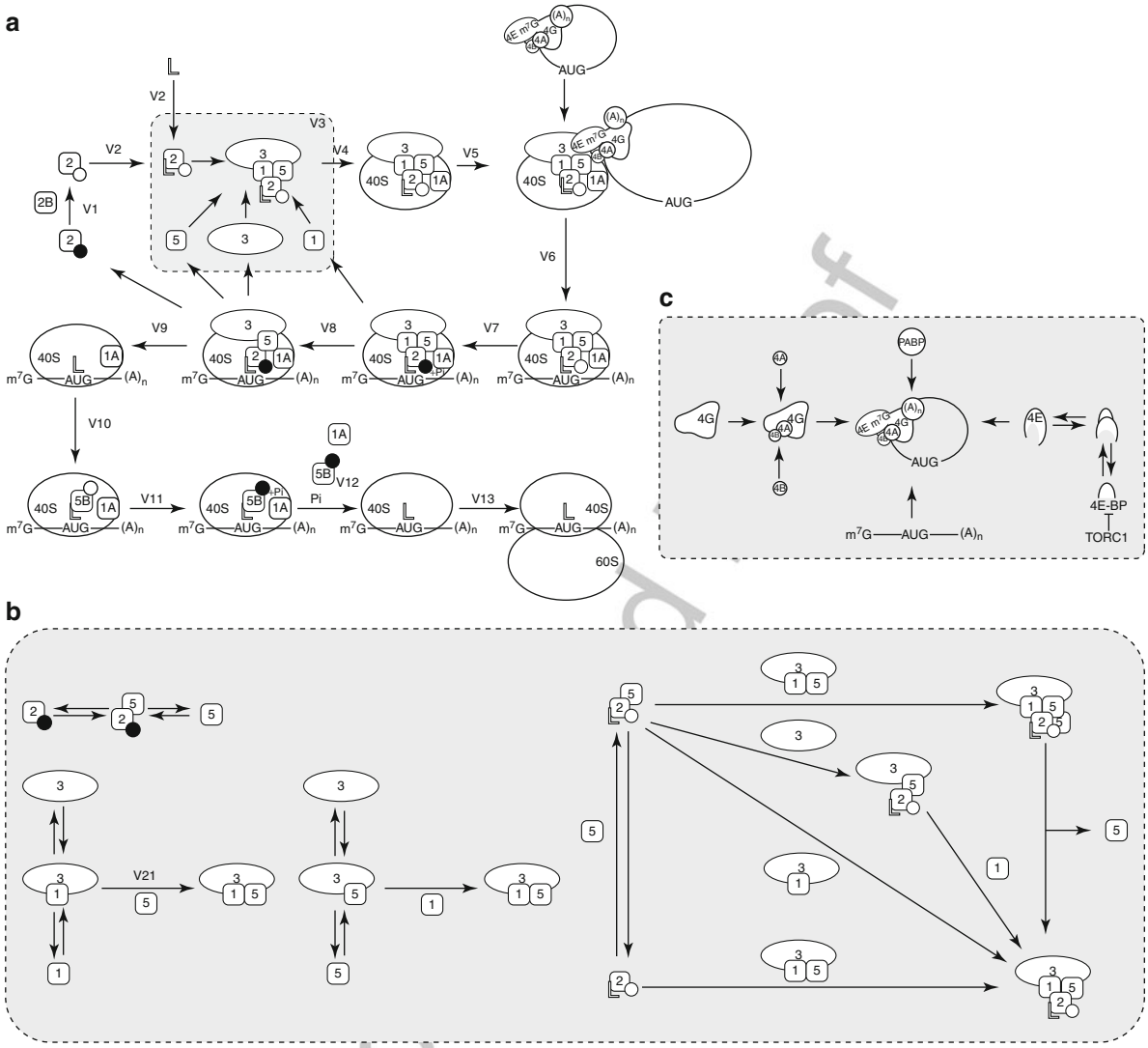
Sangthong P, Hughes J, McCarthy JE (2007) Distributed control for recruitment, scanning and subunit joining steps of translation initiation. Nucleic Acids Res 35(11):3573–3580

Singh CR, Lee B, Udagawa T, Mohammad-Qureshi SS, Yamamoto Y, Pavitt GD, Asano K (2006) An eIF5/eIF2 complex antagonizes guanine nucleotide exchange by eIF2B during translation initiation. EMBO J 25(19):4537–4546

Sonenberg N, Hinnebusch AG (2009) Regulation of translation initiation in eukaryotes: mechanisms and biological targets. Cell 136(4):731–745

von der Haar T, McCarthy JE (2002) Intracellular translation initiation factor levels in *Saccharomyces cerevisiae* and their role in cap-complex function. Mol Microbiol 46(2):531–544

You T, Coghill GM, Brown AJP (2010) A quantitative model for mRNA translation in *Saccharomyces cerevisiae*. Yeast 27(10):785–800




**Eukaryotic Translation Initiation Factor Interactions, Fig. 1** Schematic diagram of eukaryotic translation initiation