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Review

# The translational regulator eIF3a: The tricky eIF3 subunit!

Federica Saletta, Yohan Suryo Rahmanto, Des R. Richardson *

*Iron Metabolism and Chelation Program, Department of Pathology and Bosch Institute, Blackburn Building (D06), University of Sydney, Sydney, New South Wales, 2006 Australia*

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ABSTRACT

Regulation of gene expression is a fundamental step in cellular physiology as abnormalities in this process may lead to de-regulated growth and cancer. Translation of mRNA is mainly regulated at the rate-limiting initiation step, where many eukaryotic initiation factors (eIFs) are involved. The largest and most complex initiation factor is eIF3 which plays a role in translational regulation, cell growth and cancer. The largest subunit of eIF3 is eIF3a, although it is not required for the general function of eIF3 in translation initiation. However, eIF3a may play a role as a regulator of a subset of mRNAs and has been demonstrated to regulate the expression of $p27^{kip1}$, tyrosinated α-tubulin and ribonucleotide reductase M2 subunit. These molecules have a pivotal role in the regulation of the cell cycle. Moreover, the *eIF3a* mRNA is ubiquitously expressed in all tissues at different levels and is found elevated in a number of cancer types. eIF3a can modulate the cell cycle and may be a translational regulator for proteins important for entrance into S phase. The expression of eIF3a is decreased in differentiated cells in culture and the suppression of eIF3a expression can reverse the malignant phenotype and change the sensitivity of cells to cell cycle modulators. However, the role of eIF3a in cancer is still unclear. In fact, some studies have identified eIF3a to be involved in cancer development, while other results indicate that it could provide protection against evolution into higher malignancy. Together, these findings highlight the "tricky" and interesting nature of eIF3a.



**Contents**



## 1. Introduction

Regulation of gene expression is a fundamental aspect of cellular physiology [1]. Furthermore, it plays a key role in disease, as abnormal gene expression is the main cause of de-regulated cell growth and cancer. The two primary regulatory processes in gene expression take place during transcription to generate mRNAs and translation to produce proteins. The translation of mRNA is mainly regulated at initiation, the rate-limiting step, where many eukaryotic initiation

*Abbreviations:* B(α)P, benzo(*a*)pyrene; DFO, desferrioxamine; Drg-1, differentiation-related gene 1; eIF, eukaryotic initiation factor; eIF3, eukaryotic initiation factor 3; eIF3a, eukaryotic initiation factor 3 subunit 'a'; IC, initiation complex; IRE, iron-responsive element; IFN, interferon; TC, ternary complex; IRES, internal ribosome entry site; NLS, nuclear localization signal; PIC, pre-initiation complex; PCI, proteasome/COP9 complex/initiation factor domain; RRM2, ribonucleotide reductase M2 subunit; UTR, untranslated region

* Corresponding author. Iron Metabolism and Chelation Program, Department of Pathology, University of Sydney, Sydney, New South Wales, 2006, Australia. Tel.: +61 2 9036 6548; fax: +61 2 9351 3429.
*E-mail address:* d.richardson@med.usyd.edu.au (D.R. Richardson).

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factors (eIFs) are involved [2]. In the last 20 years, at least 12 eIFs have been identified and described [3]. Among the eIF family, eIF3 is the largest and most complex initiation factor. It contains 13 different subunits that are designated eIF3a to eIF3m which range in size from 25 to 170 kDa (Fig. 1A), yielding a total mass of approximately 800 kDa [4].

Due to the complexity of mammalian eIF3, many studies examining the role of eIF3 in translational initiation have been conducted in yeast. Yeast eIF3 is much simpler with only five stoichiometric 'core' subunits and several 'non-core' subunits [5–7]. The essential yeast subunits (eIF3a, eIF3b, eIF3c, eIF3g and eIF3i) that constitute the conserved core

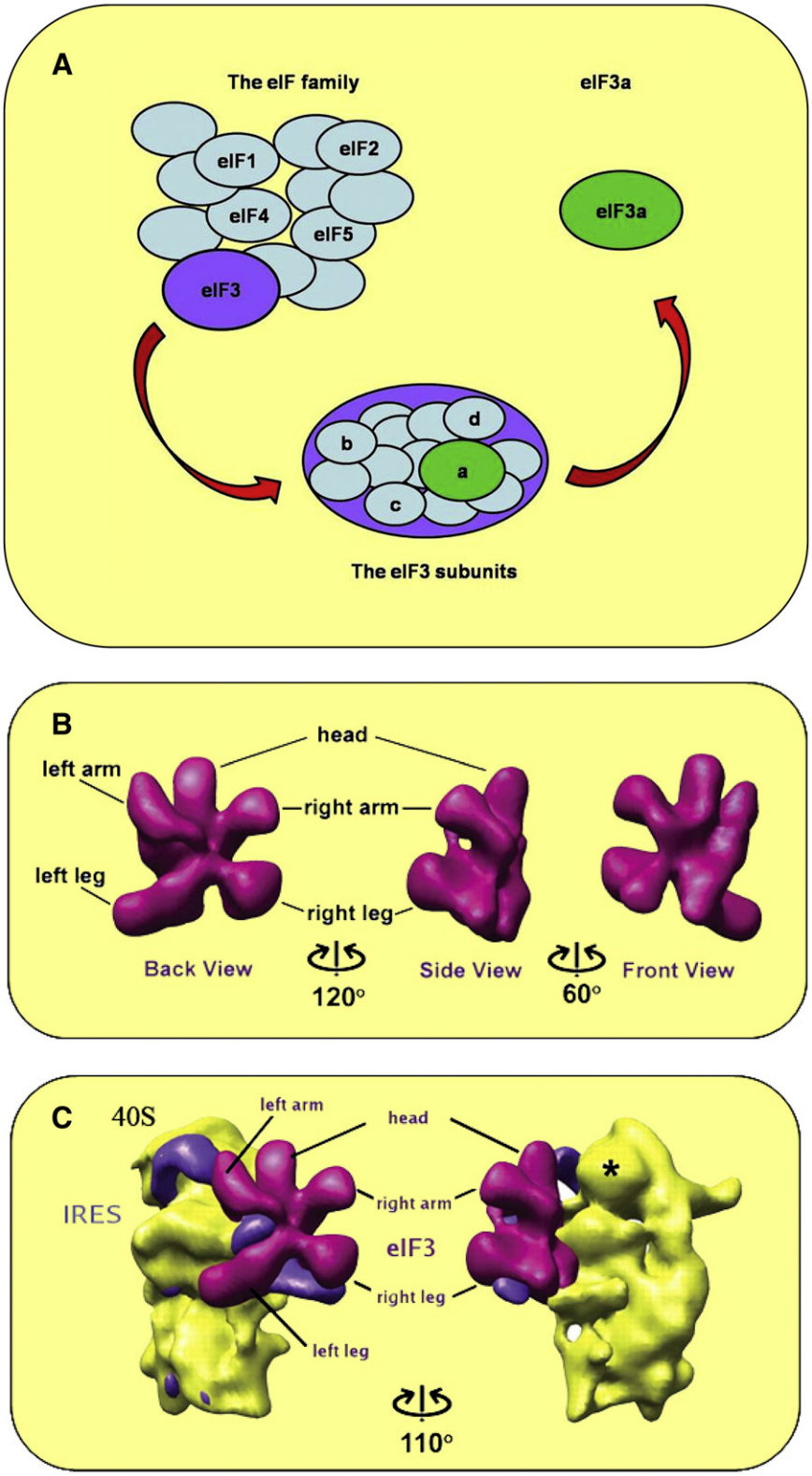


**Fig. 1.** A) From the family to the single subunit. This illustration helps to explain the intricate nomenclature of the eukaryotic initiation factors and their subunits. B) The anthropomorphic structure of eIF3. The figure shows the five-lobed structure of eIF3 (from Siridechadilok et al. [10]). C) The binding to the 40S ribosomal subunit. In this image the mechanism of contact between eIF3 and the 40S ribosomal subunit is illustrated (from Siridechadilok et al. [10]).