Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochimica et Biophysica Acta 1759 (2006) 13–31
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

eEF1B: At the dawn of the 21st century☆

Frédéric Le Sourd, Sandrine Boulben, Ronan Le Bouffant, Patrick Cormier, Julia Morales, Robert Belle, Odile Mulner-Lorillon *

Equipe Cycle Cellulaire et Développement, Unité Mer and Sante, UMR 7150 CNRS/UPMC, Station Biologique de Roscoff, BP 74, 29682 Roscoff Cedex, France

Received 29 November 2005; received in revised form 21 February 2006; accepted 22 February 2006
Available online 24 March 2006

Abstract

Translational regulation of gene expression in eukaryotes can rapidly and accurately control cell activity in response to stimuli or when rapidly dividing. There is increasing evidence for a key role of the elongation step in this process. Elongation factor-1 (eEF1), which is responsible for aminoacyl-tRNA transfer on the ribosome, is comprised of two entities: a G-protein named eEF1A and a nucleotide exchange factor, eEF1B. The multifunctional nature of eEF1A, as well as its oncogenic potential, is currently the subject of a number of studies. Until recently, less work has been done on eEF1B. This review describes the macromolecular complexity of eEF1B, its multiple phosphorylation sites and numerous cellular partners, which lead us to suggest an essential role for the factor in the control of gene expression, particularly during the cell cycle.

Keywords: Elongation factor; Gene expression regulation; Protein translation; Cancer; Virus

1. Introduction

This article is dedicated to Professor Wim Moller (Fig. 1) who passed away on the 28th of March 2005. A molecular biologist at the University of Leiden, Wim Moller's main interest was to elucidate the translation mechanism that leads to the synthesis of proteins, the real actors of the living world. While our understanding of the pathways of translation is based on experiments that began in the 1950s, Wim Moller contributed as early as 1962 [1] to the identification of ribosome structure and characterization of the factors involved in the elongation step of translation in eukaryotes using, as early as 1975, acellular extracts derived from cysts of the brine shrimp *Artemia salina* [2]. This paper highlights the important contribution of Wim Moller in the elucidation of the molecular mechanism of peptide chain elongation. Our collaboration started in 1988 and, from the beginning, it was a very friendly and kind relationship in Leiden, Paris or at his family house in Manobre, Dordogne.

Biosynthesis of proteins, the real actors of cell life, relies on a highly regulated process that begins with the transcription of DNA, the depository of genetic information, into messenger RNAs (mRNA), and ends at the level of ribosomes where the genetic information contained in mRNAs, is translated into proteins. Each step of this essential process is under strict control in order to produce the specifically required protein, in the correct amount, at the right time and in the right place. Although the regulation of gene expression is largely achieved through transcriptional control, cells have developed mechanisms of fine regulation at the level of translation to ensure direct, rapid, reversible and spatial control of protein concentration [3]. An important area of study is the regulation of translation at the initiation level, i.e., mRNA recruitment on ribosomes. On the one hand, there are reports of modifications in the amount and/or activity of translation initiation factors leading to global changes in protein synthesis. On the other hand, regulation at the level of a specific mRNA has been shown to be driven by regulatory protein complexes that recognize particular structures usually present in the 5′ and/or 3′ untranslated regions (UTRs) of mRNAs, allowing their specific recruitment for translation (reviews in [4,5]).

Although less explored, there is growing evidence of additional regulation at the level of elongation. The first

☆ This review was written in memory of Professor Wim Moller.

* Corresponding author. Tel.: +33 2 98 29 23 37; fax: +33 2 98 29 23 24.
E-mail address: mulner@sb-roscoff.fr (O. Mulner-Lorillon).

0167-4781/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbaexp.2006.02.003

Fig. 1. Dr. Wim Möller, Emerit Professor in Molecular Biology at Leiden University, 1935–2005.

indication for control of the elongation step came from the consideration that any increase in initiation activity must obviously occur in coordination with an increase in the elongation rate to avoid ribosome blockage at the level of the initiation codon. Moreover, since increases in elongation rate have been linked with increasing translational errors [6,7], it is necessary for a cell to keep elongation at the lowest rate consistent with initiation. Furthermore, there have been several reports of control of protein synthesis via the elongation rate in physiological processes such as serum or insulin stimulation (review in [8]), heat shock [9], fertilization [10,11] or morphogenesis [12]. It has been proposed that transitory inhibition of the elongation rate could be a way to globally regulate the level of short-lived proteins and to specifically favor the translation of mRNAs with weak initiation constants [13]. Although actively investigated, the mechanism(s) of translational control during the cell cycle has not yet been fully elucidated. It is well established that a number of regulatory proteins must be synthesized as required for entry and progression through the cell cycle, whereas the synthesis of the majority of proteins decreases at entry in the M-phase (review in [5]). Elongation was demonstrated to significantly contribute to protein synthesis regulation during the cell cycle [11]. In parallel, it was proposed that polyadenylation of specific mRNAs and/or translation at the level of internal ribosome entry site (IRES)-containing mRNA specifically regulate mitotic protein synthesis, although the actors involved have not all been identified (review in [14]).

Translation elongation in eukaryotes requires a set of non-ribosomal proteins called eukaryotic elongation factors or eEFs (review in [15]). They include the factors eEF1A and eEF1B, which are involved in recruitment of aminoacyl-tRNAs onto the ribosome, and the factor eEF2, which mediates ribosomal translocation. A number of reviews have recently addressed the regulation of translation by eEF1A and eEF2 [16–19]. In this report, we focus on the eukaryotic partner of eEF1A, the nucleotide exchange factor, eEF1B. The discovery of its increasingly complex macromolecular structure as well as its implication in a number of physiological processes led us to attribute a pivotal role for eEF1B in the regulation of multiple cellular functions.

2. eEF1B structure and its canonical role

In prokaryotes, EF1, the soluble factor catalyzing the transfer of aminoacyl-tRNA to ribosomes in the first step of elongation, was shown a long time ago [20] to contain two reversibly interacting components, EF-Tu (elongation factor thermo-unstable) and EF-Ts (elongation factor thermo-stable). The structural and functional properties of each subunit have been extensively studied (reviews in [15,21]). EF-Tu is a G-protein that associates in a ternary complex with GTP and aminoacyl-tRNA, to catalyze the binding of aminoacyl-tRNA to the A site ribosome via codon–anticodon interaction (Fig. 2A). Upon ribosome-dependent hydrolysis of GTP, EF-Tu is released from the ribosome under its GDP-bound form and interacts with the nucleotide exchange factor EF-Ts, which exchanges GDP for GTP to regenerate active EF-Tu. This active EF-Tu is then able to perform another round of elongation. The requirement for a guanine nucleotide exchange factor, EF-Ts, to reactivate EF-Tu is due to the 100-fold higher affinity of EF-Tu for GDP compared to GTP [22], resulting from a large structural change between the two forms of EF-Tu (review in [15]).

The characterization of eukaryotic EF1 (eEF1) has been a long process. Early purifications of the factor responsible for the transfer of aminoacyl-tRNA onto ribosomes from rat liver [23], rabbit reticulocytes [24], yeast [25], bombyx [26], calf brain

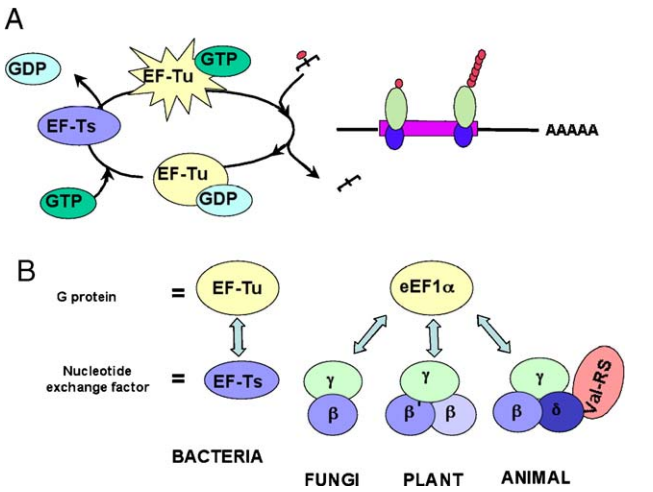

Fig. 2. First step of protein synthesis elongation. (A) Schematic representation of peptide chain elongation. The guanine nucleotide exchange factor (EF-Ts) reloads GTP on the G-protein EF-Tu which catalyzes the binding of aminoacyl (red circle)-tRNA to the A site of the ribosome (green and blue circles) associated with the messenger RNA (right) at each elongation cycle. (B) Schematic subunit composition of prokaryotic (left) and eukaryotic (right) forms of elongation factor 1. The different complexes are depicted according to the subunit composition independently from the stoichiometry. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)