Journal of Genetic and Environmental Resources Conservation, 2014, 2(3):270-282.
www.jgerc.com

Role of eEF1B subunits in regulation phosphorylation and some functions

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Abstract

In eukaryotic dominated several factors in the regulation of translation of elongation protein. Eukaryotic translation and elongation factor 1B (eEF1B) is the GTP exchange factor for eukaryotic translation elongation factor 1A (eEF1A), which is a G-protein transporting aminoacyl-tRNA to the A site of the ribosome. The GDP-GTP recycling is catalyzed by the elongation factor 1B complex (eEF1B) which in higher eukaryotes consists of three different subunits: eEF1Bα, eEF1Bδ and eEF1Bγ. All three subunits were found to be ubiquitously expressed at mRNA and protein levels in mammalian cells.

In this review we described the macromolecular complexity of eEF1B, its multiple phosphorylation sites and numerous cellular partners, providing insight into the non-canonical functions of eEF1B subunits, which lead us to suggest an essential role for the factor in the control of gene expression, particularly during the cell cycle, cytoskeleton, stress response, and the underlying mechanisms.

Keywords: eEF1B Complex, Phosphorylation, Functions, Bioinformatics.

Introduction

The process of eukaryotic protein synthesis is traditionally defined as occurring in three phases: initiation, elongation and termination, elongation factor 1 (eEF1) regulates the recruitment of amino acyl-tRNAs to the ribosome; while elongation factor 2 (eEF2) regulates ribosomal translocation (Sasikumar *et al.*, 2012). Subunits of the eEF1 complex have been named differently by different authors. The G-protein eEF1AGTP recruits amino acyl-tRNAs to the ribosomal A-site, leading to polypeptide elongation and hydrolysis of the GTP. The eEF1B complex, which is formed of α, β, and γ subunits, is required for the recycling of eEF1A-GDP back to eEF1A-GTP exchange in the eEF1A molecule, as well as the third component, Bc, which is believed to serve as a compartmentalization factor in the complex (Sanders *et al.*, 1996). eEF1Adoes not always integrate with the eEF1B complex; however, no individual subunits of eEF1B were found to exist separate from the complex under normal conditions (Brandsma *et al.*, 1995).

While eEF1Bα and eEF1Bβ are directly involved in guanine nucleotide exchange, the precise function of eEF1Bγ is less well understood. The eEF1B complex is localized to the endoplasmic reticulum, plasma membrane and cytoplasm (Sanders *et al.*, 1996; Cho *et al.*, 2003). A recent model suggests that the multi subunit complex is tethered to the endoplasmic reticulum through interactions with the endoplasmic reticulum membrane protein kinectin (Ong *et al.*, 2006).Aside from their function in the translation elongation, elements of the eEF1 complex involved in a wide variety of cellular and viral processes. In this review, we focus on the eukaryotic partner of 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 and consider their biological significance.

The translation elongation factor 1 B: Eukaryotic translation elongation factor 1B complex is responsible for the guanine exchange activity of eEF1A. In lower eukaryotes, the complex is formed by two subunits, alpha and gamma, whereas in higher eukaryotes it has an additional subunit, delta. Both eEF1Bα and eEF1Bδ have guanine nucleotide exchange activity (GEF) whereas eEF1Bγhas no known role in translation. Throughout the last few decades since this complex was first purified, the nomenclature of the subunits has constantly changed. Bearing in mind that at some point both eEF1Bα and eEF1Bδ were called eEF1beta, and for the sake of keeping this thesis as

easy to follow as possible, only one universal nomenclature (Le Sourd *et al.*, 2006).

eEF1B**α**: eEF1Bα sequence was first mapped to human chromosome 2 in 1991 by two independent groups. The sequences differed in their 5' untranslated region (UTR) but encoded an identical protein (Sanders *et al.*, 1991). Three other related sequences were mapped to chromosome 15 (eEF1B1), 5 (eEF1B3) and an X chromosome (eEF1B4). EEF1B3 locus was reported to be a brain and muscle specific transcript that arose from a pseudo gene, while eEF1B1was suggested to be a recent retro transposition event (Chambers *et al.*, 2001). The eEF1Bα protein is highly conserved throughout the eukaryotic kingdom. Gene disruption experiments in yeast showed that eEF1Bα is essential for cellular growth (Hiraga *et al.*, 1993). The catalytic site of eEF1Bα is on the C-terminus, which is responsible for binding to eEF1A and for GEF activity. eEF1Bα binding to eEF1A confers a conformational change which favors the GDP to be released so that the less abundant GTP can bind specifically to eEF1A (Andersen *et al.*, 2000). eEF1Bα protein purified from rat and rabbit liver highly stimulates the exchange of GDP to GTP on eEF1A, tRNA binding to the ribosome and phenylalanine synthesis rate (Bec *et al.*, 1994, Sheu and Traugh, 1997). eEF1Bα in yeast *Saccharomyces cerevisiae* is essential for normal survival (Hiraga et al., 1993) and interestingly, over expression of eEF1A in yeast over comes the eEF1Bα knockout lethal phenotype but the rescued yeast still possess growth defects and reduced translation fidelity (Kinzy and Woolford, 1995). The absence of the eEF1Bα GEF activity in the C terminus, but not the N terminus is responsible for the lethal phenotype and the human eEF1Bα sequence rescues the yeast eEF1Bα knockout lethal phenotype, indicating a highly conserved function (Carr-Schmid *et al.*, 1999). It is assumed that eEF1Bα helps nucleotide exchange in eEF1A by disrupting interactions between GDP with the Ploop and switch regions of eEF1A.

eEF1B**δ**: eEF1Bδ is the metazoan-specific subunit of eEF1B. The human eEF1Bδ gene is mapped to chromosome 8 which is transcribe into two mRNAs by alternative splicing. That eEF1Bδ dissociated GDP from eEF1A GDP *in vitro* at the same rate as eEF1Bα did only in the first minute of the reaction, then the nucleotide exchange rate in the system with eEF1Bδ became the same as the one without any GEF. In addition, while the presence of eEF1Bγ stimulated the nucleotide exchange activity of eEF1Bα, it did not affect the GDP dissociation catalyzed by eEF1Bδ (Bec *et al.*, 1994). The N-terminal domain of eEF1Bδ has a leucine zipper motif, indicating a possible binding of other proteins, but this motif is not involved in the polymerization of eEF1Bδ monomers (Sheu and Traugh, 1997), and the N-terminal domain is not sufficient for the dimerization of eEF1Bδ (Mansilla *et al.*, 2002). eEF1Bδ have been found to exist as different isoforms resulting from alternative splicing. Two isoforms with close MW have been discovered in *Xenopus laevis* oocytes (Mulner-Lorillon *et al.*, 1994),sea urchin embryo (Boulben *et al.*, 2003), which are encoded by two mRNAs, differing by the existence of a 78-base stretch inserted in the open reading frame (ORF), in front of the leucine zipper-encoding sequence.

Recent studies have identified another isoform for eEF1Bδ protein, which is around 70-80kD, namely eEF1BδL. The mRNA encoding eEF1BδL contains an extra exon, exon 3, which is skipped in the mRNA transcripts of other isoforms. Up to now little is known about the significance of eEF1BδL, except that it is tissue specific, expressed only in the brain, spinal cord and testis, It was also demonstrated that the expression of eEF1BδL in the brain started from embryonic day 15 (Kaitsuka *et al.*, 2011).

eEF1B**γ**: eEF1Bγ is the eukaryotic specific subunit of eEF1B, the gene of which has been mapped to human chromosome 11 in 1992 (Kumabe *et al.*, 1992). It is known to have a conserved glutathione S-transferase (GST) domain, enzymes which catalyze a variety of substrates and play a role in cellular stress, but its ability to possess GST activity is controversial and will be discussed later (Koonin *et al.*, 1994). In yeast *S. cerevisiae*, two genes encode proteins homologous to eEF1Bγ, TEF-3 and TEF-4, which are not essential for growth and their knockout does not alter translation rate (Kinzy *et al.*, 1994). Although eEF1Bγ as a monomer does not affect the GEF rate, when in complex with eEF1Bα but not with eEF1Bδ, it leads to an increased GEF rate by probably changing the conformation of the eEF1A: eEF1Bα: eEF1Bγcomplex (Bec *et al.,* 1994). Together with the fact that eEF1Bγ has affinity with the cytoskeleton and membranes, has led to the suggestion that it serves as an anchor for the eEF1Bcomplex. Moreover, eEF1Bγ was found to exist as a higher form complex, possibly a trimer, in rat liver (Bec *et al.*, 1994).

The eEF1B Complex: Although the components of eEF1B are now clear, and eEF1B is considered to form a reversible macro complex with eEF1A (eEF1H) to mediate the guanine nucleotide exchange on eEF1A, yet how the three subunits of eEF1B combine together and how they interact with eEF1A remain unknown. The components ofeEF1H have been studied in various species by different

groups and several structural models have been proposed, as shown in Figure (1). However, there is much inconsistency among these models. The first structure model proposed was by G Bec and colleagues, based on *in vitro* reconstitution experiments using different combinations of the subunits purified from rabbit liver, as well as published information about eEF1H subunits from *Artemia* by other groups (Bec *et al.*, 1994). They suggested a promoter composed of valyl-tRNA and eEF1H, which were associated through eEF1Bδ. Two such promoters could bind to each other via the leucine zipper motif in the N terminus of two eEF1Bδ subunits (Figure 1. A). Later in the same year a paper studying *Artemia* had different findings (Janssen *et al.*, 1994), and suggested a structure model wherein eEF1Bγ binds to both eEF1Bα and eEF1Bδ, each of which binds to a eEF1A subunit (Figure 1. B). Proposed a model (Figure 1. C) For *Xenopus*e EF1H based on results from the analysis of native complexes instead of reconstitution experiments (Minella et al., 1998). The model proposed by GT Sheu and colleagues suggests the existence ofeEF1Bγ dimers (Sheu and Traugh, 1999). The major difference between this model and others is that each eEF1Bγ subunit binds to one eEF1Bα or eEF1Bδ subunit, not both (Figure 1. D). Another model (Figure 1. F) Was proposed by (Jiang *et al.*, 2005) according to three-dimensional research. This model, without information on the binding regions on each subunit, is in line with the one proposed by Bec et al in1994, supporting the hypothesis of eEF1Bδ dimer being a core in the complex. While eEF1A has two isoforms, none of the models above have taken the two isoforms of eEF1A into account. Mansilla and colleagues identified an interaction between eEF1B and eEF1A1 but not eEF1A2 based on a series of Y2H experiments and therefore, suggested a model of eEF1H containing eEF1A1 but not eEF1A2 (Mansilla *et al.*, 2002). The model (Figure 1. E) Is similar to the one proposed by Janssen *et al*. (1991) except that it suggests the potential of dimerizing of eEF1B via theeFE1Bδ subunit. Although the above models are different from each other, which is very likely to be caused by the different techniques used in different groups, there are some points that seem to be less controversial among all the models. Firstly, it is believed that eEF1Bα and eEF1Bγ are tightly associated and can only be separated under denaturing conditions (Bec and Waller, 1989). Secondly, eEF1Bα and eEF1Bδ showed no affinity for each other. Finally, the binding sites of eEF1Bα and eEF1Bδ to eEF1Bγ locate on the N-terminus of the three proteins, while the C-terminus of eEF1Bα and eEF1Bδ harbors the binding sites for eEF1A.

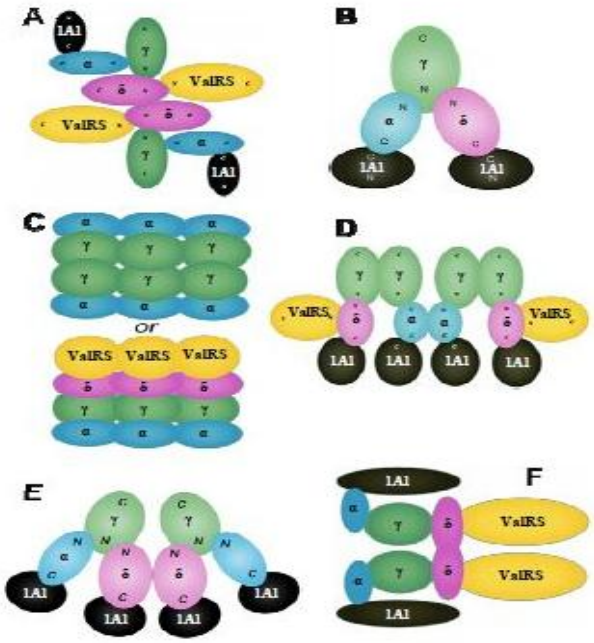

Figure (1): eEF1B complex quaternary structure models interacting with eEF1A and ValRS proposedby Bec *et al.*, 1994 (A), Janssen *et al.*, 1994 (B), Minella *et al.*, 1998 (C), Sheu and Traugh 1999 (D), Mansilla *et al.*, 2002 (E) andJiang *et al.*, 2005 (F). **α**, **δ**, **γ**, 1A1 and ValRS represent eEF1B**α**, eEF1B**δ**, eEF1B**γ**, eEF1A1 and ValRS respectively. N and C represent N-terminus and C-terminus of the subunit respectively.

Role of eEF1B subunits in Regulation phosphorylation: There are multiple reports on the

ability of eEF1B subunits to be phosphorylated by protein kinases, a major way to modulate protein and cellular activities, and eEF1B subunits have been shown to be phosphorylated *in vivo* and *in vitro* by different protein kinases, mainly on the serine or threonine residues. eEF1Bα and eEF1Bδ, together with ValRS and eEF1A, are phosphorylated by protein kinase C (PKC) in response to the stimulation of hormones such as 4Pphorbol 12-myristate 13-acetate (PMA) in rabbit reticulocytes; this stimulated elongation activity up to three fold both *in vitro* and *in vivo* (Venema *et al.*, 1991). It is then found that this phosphorylation by PKC of eEF1Bα and eEF1Bδ increased the rate of nucleotide exchange and of Phe-tRNA binding to ribosomes, and thus stimulated elongation activity (Peters *et al.*, 1995).

In the presence of little or no eEF1A, phosphorylation of purified eEF1Bα and eEF1Bδ by S6K leads to an increase in phenylalanine synthesis and tRNA binding to the ribosomes by more than 2 fold compared with serum-deprived mouse 3T3 cells (Chang and Traugh, 1997). All phosphorylation sites on both eEF1Bα and eEF1Bδ are the same for insulin- andS6K-induced phosphorylation (Chang and Traugh, 1998). Phosphorylation of eEF1Bα and eEF1Bδ were stimulated by PMA to a similar extent as that found with insulin, and the phosphorylation sites were found to be identical. eEF1Bα, eEF1Bγ and eEF1A1 were identified, by microarray study and confirmed by real time PCR, as being regulated in a serum and rapamycin-dependent way by tuberous sclerosis1 and 2, TSC1 and TSC2. Moreover, all human eEF1B genes have 5' terminal oligopyrimidine track (5' TOP) upstream, a stretch of pyrimidine residues that act as cis-acting modulators of translation efficiency and were thought to be regulated by S6K1. However TSC1/2 and mTOR affect the translation via phosphorylation of S6K1 independently from the 5' TOP status (Iadevaia *et al.*, 2008).

Both eEF1Bδ and eEF1Bγ in *Xenopus* oocytes are major maturation promoting factor (or cell division cycle p38 cdc2) substrates (Mulner-Lorillon *et al.*, 1994). eEF1Bγ was found to be phosphorylated by p38 cdc2 in mature oocytes but not in prophase-arrested oocytes. This phosphorylation resulted in decreased rates of incorporation (synthesis) of the Valine and increased synthesis of serine and phenylalanine (Monnier *et al.*, 2001) but did not alter the guanine exchange rate (Mulner-Lorillon *et al.*, 1989). Monnier suggested that p38 cdc2 inactivated eEF1B: VARS leaving more freely available eEF1B for protein synthesis (Monnier *et al.*, 2001). Activation of p38 cdc2 is involved in the progression into mitosis and the exit of mitosis involved in activation.

Brine shrimp eEF1Bα along with *Xenopus* and rabbit eEF1Bα and eEF1Bδ are phosphorylated by casein kinase II (CKII) (Chen and Traugh, 1995, Palen *et al.*, 1994, Janssen *et al.*, 1988). CKII phosphorylation of eEF1Bδ was only seen in the presence of GDP, whereas eEF1Bα phosphorylation was stimulated by GDP, lysine and arginine (Palen *et al.*, 1994). No change was observed in the phenyalanine synthesis rate upon CKII phosphorylation of rabbit recombinant eEF1Bα or eEF1Bδ proteins (Chen and Traugh, 1995). However, in the brine shrimp phosphorylation by CKII of eEF1Bα leads to an increase in eEF1A:GDP of about 50% (Janssen et al., 1988). Furthermore, CKII is phosphorylated and activated by p34 cdc2 in a cell cycle dependent manner upon stimulation by growth factors (Homma and Homma, 2005). CKII knockout in yeast and mouse is lethal and besides its involvement in the cell cycle, CKII also phosphorylates a wide range of targets upon stress and DNA damage (Ahmed *et al.*, 2002). eEF1Bδ is known to be phosphorylated by herpes simplex virus (HSV-1) UL-13 kinase, cytomegalovirus (CMV) UL-97 kinase and Epstein-Barr virus (EBV) BGLF4 kinase upon viral infection. The eEF1Bδ phosphorylation site was identified as being the same site that is phosphorylated by cdc2, suggesting that viral kinases might mimic cdc2 in infected cells (Kawaguchi *et al.*, 2003). eEF1Bδ is also known to interact with a transactivator of HSV-1, infected cell protein 0 (ICP0). Co immunoprecipitation of ICP0 and eEF1Bδ results in a decrease in the rate of incorporation of methionine compared to precipitation of eEF1Bδ alone. The down-regulation of eEF1A or eEF1G by treating cells with siRNA leads to sharply reduced efficiency of HIV-1reverse transcription in vitro, as depletion of eEF1 subunitseEF1A and eEF1G ablated the ability of active protein fractions to stimulate late steps of HIV-1 reverse transcription (Warren et al.,2012). It is also known that the eEF1Bδ interaction with HIV-1 Tat mRNA highly reduces the methionine incorporation rate, but not that of viral protein synthesis. Regulation of eEF1B subunits might play an important role in mitotic translation and translation during viral infection.

eEF1Bγ was also found to be phosphorylated following the addition of the chemotherapy drug Paclitaxel (Taxol) which stabilizes microtubules and causes G2/M arrest-induced apoptosis via c-Jun N-terminal kinase (JNK) activation and B cell lymphoma protein 2 (Bcl-2) phosphorylation. Yeast eEF1Bα dephosphorylation by Ppz1 phosphatase enhances translation fidelity in vitro (Aksenova *et al.*, 2007). In addition, all eEF1B subunits were

found to be up regulated by Myc over expression in human and chicken tumor cells (Boon *et al.*, 2001; Neiman *et al.*, 2001). However, in non-transformed rat and mouse cells, no change was observed in eEF1B subunits when comparing Myc overexpressing cells to Myc null cells (Watson *et al.*, 2002) suggesting that up-regulation might be a due to the transformed cancer cell rather than a direct effect of myc overexpression.

Some functions of eEF1B: There is a range of functions carried out by the eukaryotic translation elongation factor 1B complex as shown in Figure (2).

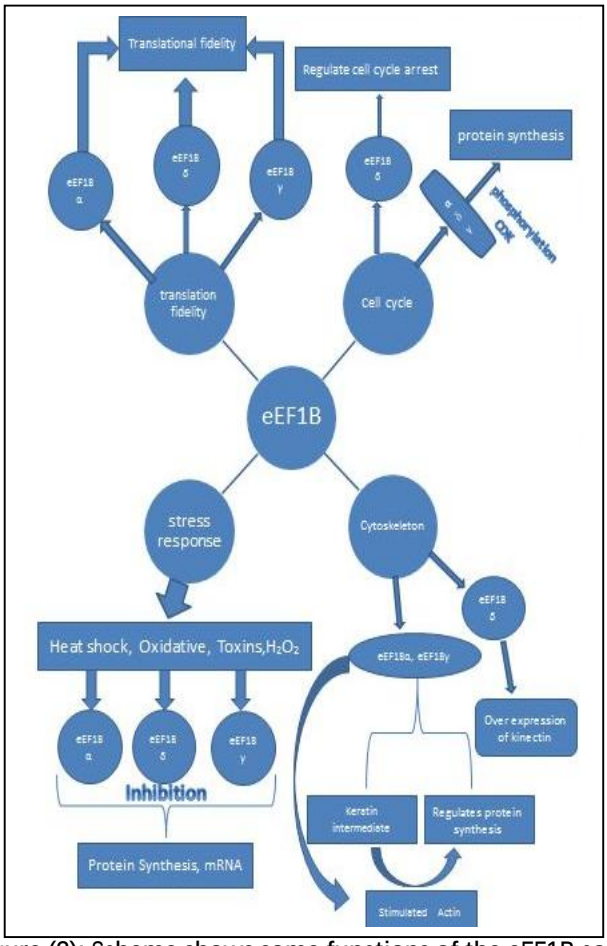

Figure (2): Scheme shows some functions of the eEF1B complex

eEF1B and the cell cycle control: The cell cycle is controlled mainly through CDKs (Murray, 2004), which are regulated by cyclical proteolysis of cyclins by phosphorylation cascades. eEF1B subunits are regulated by kinases that are involved in the cell cycle, including CDK1 and PKC, and the phosphorylation ofeEF1B subunits by some kinases coincide with the reduced protein synthesis activity during mitosis. In addition, other lines of evidences also suggest that eEF1B plays a role in cell cycle control. And eEF1Bα regulates the activity of actin assembly of eEF1A, which is important for maintaining the structure of the loop contractile during cytokinesis, two proteins, CF51 and CF32, which were found to be enriched in the furrow division (CF) isolated from the division of the egg sea urchin as eEF1A and eEF1Bα (Fujimoto and Mabuchi 2010). Furthermore, in sea urchin early embryonic cell cycles the eEF1Bδ protein level does not change, although a fraction of eEF1Bδ change location in a cell cycle specific manner, the total expression level does not change. At the time of nuclear envelope break down during mitosis, a fraction of eEF1Bδ concentrates around the nucleus and later forms two large spheres around the mitotic spindle poles, suggesting a link between eEF1Bδ and cell cycle regulation (Boulben *et al.*, 2003). In HeLa cells undergoing mitosis, the two shorter isoforms of endogenous eEF1Bδ protein change their intensities around the M-phase, with a shift of the lower to the upper band (Sivan *et al.*, 2011), indicating a cell cycle dependent alternative splicing of eEF1Bδ mRNA. Human squamous carcinoma cells SCC-35 exposed to ionizing

radiation express an elevated level of eEF1Bδ and are arrested at G2/M transition, indicating a role of eEF1Bδ in cell cycle dependent response to DNA damage (Jung *et al.*, 1994).

eEF1B and the cytoskeleton: Cytoskeletal filaments in eukaryotic cells are divided into three main types of microtubules, intermediate filaments, and microfilaments, each of which has been found to be associated with different subunits of eEF1B, suggesting the roles of eEF1B and the regulation of cytoskeleton may be closely related. A 17 kD fragment of *Dictyostelium discoideum* eEF1Bα was found to associate with actin in vitro, and recombinant *Dictyostelium discoideum* eEF1Bα expressed in E. coli stimulates the assembly of actin (Furukawa *et al.*, 2001), whereas eEF1Bα and actin extracted from sea urchin eggs show no affinity to each other (Fujimoto and Mabuchi 2010). First group proposed that eEF1Bα balances, the roles of eEF1A between translation and actin organization by competing with actin for the binding site on eEF1A (Pittman *et al.*, 2009), while another group found that eEF1Bα disrupts the eEF1A-induced actin bundling by promoting guanine nucleotide change on eEF1A (Fujimoto and Mabuchi 2010). Nevertheless, the observation that eEF1Bα disrupts eFE1A-induced actin bundling may to some extent explain the observation that eEF1Bα stimulates the rate of actin assembly in a concentration dependent negative manner (Furukawa *et al.*, 2001). However, the same report found that unlike eEF1Bα alone, the intact eEF1Bα:eEF1Bγ complex stimulated actin assembly in a concentration dependent manner (Furukawa *et al.*, 2001), indicating eEF1Bγ is likely to play a role in actin assembly. Microtubules are also found associated with eEF1B. eEF1Bα and eEF1Bγ are often associated with tubulin in *Artemia*, and under non-denaturing conditions eEF1Bγ co precipitated with tubulin (Janssen and Moller, 1988). Kinectin is a microtubule-dependent membrane anchor, and eEF1Bδ has been found to interact with kinectin both in vivo and in vitro. Overexpression of kinectin fragments in vivo disrupts the subcellular localization of eEF1Bδ but not the ER network, indicating its potential role as the anchor of the eEF1B complex to the ER (Ong et al., 2003). Interruption of kinectin binding to eEF1Bδ decreases the expression of membrane protein, but enhances cytosolic protein expression, It was found binding of eEF1Bδ to certain components of the cytoskeleton regulates protein synthesis, while two other subunits of eEF1B were not interact with kinectin in Y2H and coIP experiments (Ong *et al.*, 2006).

During the division of fertilized sea urchin eggs, were found eEF1Bδ translation with astral microtubules but not spindle microtubules in metaphase, anaphase and telophase, and proven through the distribution division eEF1Bδ to rely on microtubules (Boulben *et al.*, 2003) eEF1Bγ is usually considered as a scaffold subunit for the eEF1B complex, as it has no guanine nucleotide exchange activity, and the deletion of eEF1Bγ in *S.cerevisiae* does not affect protein synthesis or translation fidelity in vivo (Olarewaju *et al.*, 2004). However, disruption of eEF1Bγ binding to keratin, which is an intermediate filament of the cytoskeleton, leads to decreased protein translation in human epithelial cells (Kim *et al.*, 2006; Kim *et al.,* 2007)

eEF1B and the stress response: Stress conditions include several variables, radiation, temperature changes, and the exposure of drugs or toxins, oxidative stress, hypoxia and reduction of nutrients. Cells exposed to conditions emphasize the expression of genes that respond to stress in order to adapt to the circumstances (Holcik and Sonenberg, 2005).

Research has identified a protein eEF1Bα and eEF1Bδ as potential candidates that respond to heat and shock may be involved in signaling pathways of heat shock in RIF-1 cells (Kim *et al.*, 2002). eEF1Bα is down regulated in MCF, HCT116 and H460 cell lines exposed to ionizing radiation (IR) (Byun *et al.*, 2009). Also observed down regulation of eEF1Bα at all levels of the mRNA and protein, in rice after heat shock (Lin et al., 2005). The RNA-binding protein TIAR suppresses translation in RKO cells in response to low levels of short-wavelength UV (UVC), by binding to the 3'UTR of the mRNAs of eEF1Bα, as well as eIF4 A, eIF4 E, but not eEF1Bδ or eEF1Bγ (Mazan-Mamczarz *et al.*, 2006). Down regulation of eEF1Bα also occur after exposure to H2O2 in S. cerevisiae (Godon *et al.*, 1998). Moreover, H_2O_2 in *S. cerevisiae* leads to protein S-thiolation of eEF1Bα in response to oxidative stress (Shenton and Grant 2003), and loss of eEF1Bα results in greater resistance to CdSO4 (Olarewaju *et al.*, 2004).

In contrast eEF1Bα, which is down regulated in response to ionizing radiation, in SCC-35 cells exposed to the same radiation eEF1Bδ has been found up regulated (Jung *et al.*, 1994). eEF1Bδ is also up regulated in 3T3 cells transformed by cadmium. Moreover, the overexpression of eEF1Bδ in the line of human melanoma cell MeWo show resistance to chemotherapy antineoplastic drugs, such as Vindisin, cisplatin, etoposide and fotemstine (Sinha *et al.*, 2000). A recent study found that the tissue-specific alternative splicing is likely to be a way to coordinate the roles eEF1Bδ translator in response to heat shock (Kaitsuka *et al.*, 2011), heat

shock in HEK293 cells leads to the organization consists of eEF1BδL to regulate the expression of heat shock element (HSE) containing heat shock genes resulting from the transcription factor (HSF1). The association of eEF1A with HSF1 has been identified in mammalian cell extracts, which was enhanced by heat shock. It is suggested that eEF1A1, together with heat shock RNA (HSR) 1, regulates the trimerization and trigger the activation of HSF1 (Shamovsky *et al.*, 2006). On the other hand, eEF1BδL, although the expression may not be restricted to only the motor neurons, induces the expression of HSE-containing genes in cooperation with HSF1 but not by activation of HSF1 (Kaitsuka *et al.*, 2011).

As well as, eEF1Bγ, plays an important role in oxidative stress response. The N-terminal of eEF1Bγ has a structure similar to a class of Theta GSTs (Koonin *et al.*, 1994), which is important for cellular detoxification of reactive oxygen species (ROS). Whether the GST-like domain of eEF1Bγ contains full GST activity is still to be determined. Rice recombinant eEF1Bγ and the eEF1B complex, both show a low GST activity (Kobayashi *et al.*, 2001). eEF1B from Leishmania major is able to discharge a variety of substrates for trypanothione electrons which is a substrate similar to glutathione (Vickers *et al.*, 2004). Additionally, the GST-like domain is possibly involved in the detoxification of lipophilic compounds. Over expression of eEF1Bγ in parasite Trypanosoma cruzi leads to the resistance of clomipramine and antidepressant drug (Billaut-Mulot *et al.*, 1997).

Studies have also found that strains lacking eEF1Bγ show increase the level of oxidized proteins, and defects in protein turnover and vacuolar functions in response to oxidative damage (Esposito and Kinzy, 2010). Furthermore, TEF3-encoded protein regulates methionine sulfoxide reductase A (msrA), and plays an important role in the adaptive response of yeast to oxidative stress, by linking their promoter.

eEF1B and translation fidelity: The yeast *S. cerevisiae* eEF1Bα knockout was lethal, but a lethal phenotype can be overcome by over expression of eEF1A, which led to slow growth and reduce translational fidelity (Kinzy and Woolford, 1995). Transformations in the eEF1Bα GEF domain lead to a decreased translation rate and increased translation non-sense suppression in all three nonsense codons (Carr-Schmid *et al.*, 1999). Mutations that have been identified by further investigation were influenced by the rate of translation, but not necessarily fidelity (Andersen et al., 2000). eEF1Bα was shown to play a critical role in translational fidelity (Carr-Schmid *et al.*, 1999). Over expression of eEF1Bα overcomes the protein phosphatase Ppz1 over expression, slow growth phenotype by interacting with Ppz1. In yeast, over expression of eEF1A and eEF1Bα does not affect fidelity, however, when co-expressed their increase fidelity (Munshi *et al.*, 2001). Over expression of eEF1Bγ does not alter GEF rate (Carr-Schmid *et al.*, 1999) but causes loss of non-sense suppression hence reduced fidelity (Benko *et al.*, 2000). Several factors regulate translation, including eEF1A, also cause changes in the translation fidelity (Munshi *et al.*, 2001).

Bioinformatics of eEF1B: *In silico* prediction and analysis of eEF1B subunits characteristics involved a variety of web tools and software. BLAST searches were carried out with the eEF1B subunits' DNA, mRNA or protein sequences against GenBank databases (Benson *et al.*, 2012). None of the tools predict the structure of genes different from those already known for each of the subunits eEF1B. In short, bioinformatics is a management information system for molecular biology and has many practical applications.

The aims of bioinformatics are organised data in a way that allows researchers to access existing information and to submit new entries as they are produced, such as, the 3D macromolecular structures for Protein Data Bank. The second aim is to develop tools and resources that aid in the analysis of data. For instance, having sequenced a particular protein, it is of benefit to compare it with previously characterised sequences. This needs more than just a simple text-based search and programs such as FASTA (Pearson and Lipman, 1988) and PSI-BLAST (Altschul *et al.*, 1997) must consider what comprises a biologically significant. The third aim is to use tools to analyse the data and interpret the results in a biologically meaningful manner. Usually, biological studies examined individual systems in detail, and often compared them with just a few of which are relevant. In bioinformatics, recently conduct global analyses of all the available data with the aim of uncovering common principles that apply across many systems and highlight novel features.

Protein sequence databases: Classified databases protein sequence to the primary, secondary or compound. Preliminary data bases containing more than 300,000 protein sequence and function as a repository of raw data. Some stores are more common, such as SWISS-PROT and PIR International (McGarvey *et al*., 2000), annotate the sequences as well as a description of the functions of proteins and the building domain, and post-translational modifications. Composite databases such as OWL (Bleasby *et al.,* 1994) and the NRDB (Bleasby and

Wootton, 1990) Translate the data sequence and the candidate of the primary databases to produce different groups of combined non-redundant, which is more complete than the individu al databases include data sequence of the protein coding regions are translated in the databases of DNA sequences. While, the secondary databases contain information derived from the sequence of the protein and help the user determine whether a new sequence belongs to the family of a protein known. One of the most popular is PROSITE (Hofmann *et al.,* 1999), a database of short sequence patterns and profiles that characterize biologically significant sites in proteins. Prints (Attwood *et al.*, 2000) offered in this concept, a compendium of protein fingerprints conservation groups of motifs that characterize protein family. Usually are separated motifs along the protein sequence, but may be contiguous in 3D space when it is folded protein. Using several motifs can be encoded fingerprints of protein folds and functions more flexible than PROSITE. Finally, Pfam (Bateman *et al.*, 2000) contains a large collection of multiple sequence alignments and profile Hidden Markov Models covering many common protein domains. PFAM-A includes precise alignments collected manually while, PFAM-B is a compilation of automated full database SWISS-PROT. Low complexity and disordered regions were predicted by SEG, and the ability to form disulphide bonds was predicted by Predict Protein DiSulFind (Ceroni *et al.*, 2006). To predict the ability to direct a particular organelle Signal P 3.0 prediction was carried out (Emanuelsson *et al.*, 2007). Identified the structural properties of proteins by synchrotron small angle X-ray scattering (SAXS) and analytical ultracentrifugation (Timchenko *et al.*, 2013).

Structural databases: The Protein Data Bank, PDB, provides a primary archive of all 3D structures for macromolecules such as proteins, RNA, DNA and various complexes. Most of the ~13,000 structures are solved by x-ray crystallography and nuclear magnetic resonance (NMR), but also included some theoretical models. As the information contained in individual PDB entries can be difficult to extract, PDB sum (Laskowski *et al.,* 1997) provides a separate Web page for every structure in the PDB displaying detailed structural analyses, diagrams and data on interactions between different molecules in a given entry. Three major databases rating by the structure of proteins in order to determine the structural and evolutionary relationships: CATH (Pearl *et al.,* 2000), SCOP, and FSSP databases (Holm *et al.*, 1998). Include all structural hierarchical classification in terms of increasing groups of proteins in the similarity in the lower levels of the tree classification. In addition, numerous databases focus on particular types of macromolecules. The database includes these nucleic acids NDB for structures related to nucleic acids, the HIV protease database (Vondrasek and Wlodawer, 1997) for HIV-1, HIV-2 and SIV protease structures and their complexes, and ReLiBase (Hendlich, 1998) for receptor-ligand complexes.

Protein-protein interactions: Generally, proteins must interact with each other to carry out the biochemical. Thus, mapping out protein-protein interactions is another important aspect of proteomics. Protein interactions are considered among the strong interactions that allow the formation of stable complexes and weaker ones that exist transient. Proteins involved in the formation of complexes are usually more tightly co regulated in expression of those involved in transient interactions.

Proteins can react with other proteins to form pathways and these interactions are stored in specific databases. APID2NET (Hernandez-Toro *et al.,* 2007) and CytoScape (Cline *et al.,* 2007) integrate several of these databases. All the protein-protein interaction information for each eEF1B subunit was combined and visualized using CytoScape. BINGO CytoScape plugin (Maere *et al.,* 2005) was used to retrieve. The gene ontology classifications of all the interactors and compared them to the gene classification frequencies in the human genome (Ashburner *et al.,* 2000).

Conclusions

This review sheds light into the considerably more intricate role of eEF1B in translation than previously understood, the potential vital importance of functionseEF1B subunits. More studies are needed to clarify the involvement of eEF1B subunits in translation and possible non-canonical functions such as, cytoskeleton remodeling, cell cycle regulation, stress response, translation fidelity and the significance of different isoforms of eEF1B.

Acknowledgments

This study was financially supported by Major State Basic Research Development Program of China (973 Program, No. 2011CB100804), 863 Project of Ministry of Science and Technology of China (No: 2013AA102504-03).

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