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The translation elongation factor 1A in tumorigenesis, signal transduction and apoptosis: Review article

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Summary. An increasing number of evidences suggest the involvement of the eukaryotic elongation factor 1A, a core component of the protein synthesis machinery, at the onset of cell transformation. In fact, eEF1A is shown to be up-regulated in cell death; moreover, it seems to be involved in the regulation of ubiquitin-mediated protein degradation. In addition, eEF1A undergoes several post-translational modifications, mainly phosphorylation and methylation, that generally influence the activity of the protein. This article summarizes the present knowledges on the several extra-translational roles of eEF1A also in order to understand as the protein synthesis regulatory mechanisms could offer tools for cancer intervention.

Keywords: Translation elongation factor 1A – Protein synthesis – Ubiquitin – Interferon α

Abbreviations: eEF, eukaryotic elongation factor; PTI-1, prostate tumor-inducing 1 gene; eIF, eukaryotic initiation factors; IFN, interferon; EGF, epidermal growth factor

Introduction

In eukarya, bacteria and archaea (Woese et al., 1990) the protein synthesis process follows the same general scheme (Miller and Weissbach, 1977; Riis et al., 1990). During evolution, this process has undergone significant changes especially in eukaryotic organisms. In fact, protein synthesis is one of the most complicated biochemical process occurring in the cell which requires several hundreds of different proteins and different RNAs. An increasing series of data are presently emerging about the involvement of translation factors in the control of cell proliferation, thus suggesting that protein synthesis can be an additional target for anti-cancer strategies (Caraglia et al., 2000). The translation process consists of three phases: initiation, elongation and termination. The control of protein biosynthesis at level of the initiation step is well recognised to play an important role. In fact, several factors involved in protein synthesis have shown until today to have regulatory properties such as the initiation factors eIF2, eIF2B, eIF4E, eIF4G, eIF5A (Sonenberg, 1993; Rhoads, 1999; Caraglia et al., 2000). However, many studies indicate that in eukaryotic cells the control at the elongation level can likewise be important during the cell cycle (Moldave, 1985), heath shock (Rattan et al., 1988), treatment with phorbol ester (Gschwendt et al., 1988), hormons and mitogens (Rhoads, 1993; Frederickson and Sonenberg, 1992; Hershey, 1991), growth factors (Thomas and Thomas, 1986), aging (Cavallius et al., 1986) oxidative stress (Ayala et al., 1996). In this view the elongation factors 2 (eEF2), whose activity is modulated by post-translational modifications such as ADP-ribosylation (Fendrick and Iglewski, 1989) and phosphorylation (Hovland et al., 1999; Diggle et al., 1998) seems to be involved in the regulation of proliferation. Also the expression of the elongation factor 1A (eEF1A, formerly EF-1α) (EF-Tu in eubacteria) (see Clark et al., 1996 for the suggested new nomenclature) is depending on the physiological cellular conditions. In fact, eEF1A levels decrease during aging in mouse and human fibroblasts (Cavallius et al., 1986) whereas, in *Drosophila melanogaster*, if constitutively expressed, increases its lifespan (Shepherd et al., 1989).

The eukaryotic elongation factor 1A catalyzes the first step of the elongation cycle (Moldave, 1985; Klink, 1985; Kaziro, 1991). It carries the aminoacyl-tRNA (aa-tRNA) on the A site of the ribosome which contains the growing

polypeptide chain as peptidyl-tRNA in the P site. The aa-tRNA is carried on the ribosome as a ternary complex eEF1A · GTP · aa-tRNA and, following the hydrolysis of GTP, the eEF1A · GDP leaves the ribosome. This event allows the correct positioning of aa-tRNA in the A site of the ribosome in response to a correct codon-anticodon recognition. The second step of the elongation cycle involves the regeneration of the inactive GDP-bound form of EF1A into the active GTP-bound form through an exchange reaction catalysed by the exchange factor 1Bα (eEF1Bα) (EF-Ts in eubacteria). After the formation of a new peptide bond catalysed by the ribosomal peptidyl-transferase, a peptidyl-tRNA is present on the A site of the ribosome and a deacylated tRNA in the P site (ribosome in pre-translocative state). In the third step of the elongation cycle, translocation, the elongated peptidyl-tRNA moves from the A site to the P site of the ribosome. The reaction is catalysed by the elongation factor 2 (EF-G in eubacteria). Both EF1A/EF-Tu and EF2/EF-G belong to the class of GTP binding proteins (Dever et al., 1987), characterized by a molecular switch from an active conformation bound to GTP to an inactive conformation bound to GDP. Following the hydrolysis of GTP, the complex eEF2 · GDP leaves the ribosome, thus ending the translocation reaction. One elongation cycle is now completed and the machinery is ready to initiate a new cycle (Fig. 1).

The function and structure of eEF1A has been investigated mainly in eubacteria (*Escherichia coli* EF-Tu) (Krab and Parmeggiani, 1998) but also in archaea (Arcari et al., 1994; Vitagliano et al., 2001). EF-Tu/EF1A is a monomeric enzyme made of three structural domains (Kjeldgaard and Nyborg, 1992; Kjeldgaard et al., 1993; Berchtold et al., 1993; Nyborg, 1998; Andersen et al., 2000; Andersen et al., 2001). *E. coli* EF-Tu possesses other functional properties; it is a subunit of the Qβ replicase, it acts as chaperonin in the renaturation of rodhanase, and displays a disulfide isomerase activity (Krab and Parmeggiani, 1998; Nyborg, 1998).

eEF1A and tumorigenesis

Beside to its central role in translation, eEF1A plays in eukaryotic cell a large number of other functions (Negrutskii and El'skaya, 1998). eEF1A forms complexes with other cellular components like tubulin and actin, whose functions are yet unclear (Condeelis, 1995; Betkas et al., 1994). In addition, eEF1A is known to be involved in several cellular process, including embryogenesis, senescense, oncogenic transformation, cell proliferation and organization of cytoskeleton (Gangwani et al., 1998). Altered expression of eEF1A have been linked to transformed phenotypes in several independent studies and in different systems (Wang et al., 1997; Gopalkrishnam et al., 1999). In fact, the role of eEF1A in oncogenesis has been investigated in prostate carcinoma. In these tumoral cells, a dominant oncogene has been identified: PTI-1 (tumor inducing-gene 1). The expression of PTI-1

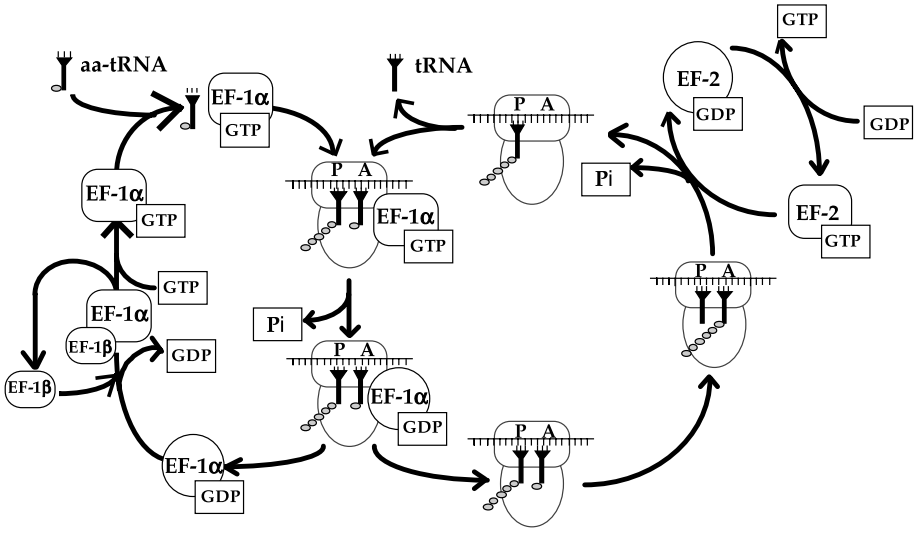

Fig. 1. Protein synthesis elongation cycle. Role of eEF1A, eEF1Bα and eEF2 in the first, second and third step of the elongation cycle, respectively. *aa-tRNA*, aminocyl-tRNA; *EF-1*α, elongation factor 1A; *EF-1*β, elongation factor 1Bα; *EF-2*, elongation factor 2; *A* and *P*, ribosomal A and P site, respectively

occurs also in breast, colon and lung carcinoma cell lines, but not in normal cells. The full length PTI-1 cDNA is 2123 bp, consisting of a unique 630 bp 5′UTR with significant homology to *Mycoplasma hyopneumoniae* 23S ribosomal RNA fused to a sequence that is truncated N-terminal and with six point mutations corresponding to human elongation factor EF1A (Gopalkrishnam et al., 1999). Blocking PTI-1 expression with antisense-PTI-1 resulted in reversion of transformed PTI-1 expressing cells to a more normal cellular fenotype. Expression studies have confirmed the oncogenic nature of the molecule. A broad spectrum of tumor derived cell lines, from different tissue sources and blood samples from patients with prostate carcinoma, were positive for expression of PTI-1, while corresponding normal tissues or blood samples were negative. Therefore, it has been proposed that PTI-1 represents a new class of oncogene whose transforming capacity probably arises through mechanisms including: (i) protein translational infidelity, resulting in the synthesis of mutant polypeptides due to the loss of proof-reading function during peptide chain elongation (Zao-zhong et al., 1998), (ii) its association with cytoskeleton, as well as the alteration of the latter, (iii) impinging on one particular or several different signal transduction pathways through its properties as a G-protein (Gopalkrishnam et al., 1999). Furthermore, overexpression of EF1A mRNA has been correlated with increased metastatic potential in mammary adenocarcinoma probably due to its interaction with the actin cytoskeleton, an effector in metastasis (Edmonds et al., 1996). It has been shown that eEF1A protein is overexpressed in metastatic cells compared to nonmetastatic ones, and that eEF1A from metastatic cells has a reduced affinity for F-actin. Following stimulation with EGF, there is a parallel increase in the amount of F-actin and eEF1A associated with the cytoskeleton. Therefore, it has been proposed that a weakened association of eEF1A with actin may be related to the metastatic process via an altered organization of the actin cytoskeleton and the differential translation of mRNAs associated with the cytoskeleton (Edmonds et al., 1996).

eEF1A and apoptosis

eEF1A is also reported to be involved in apoptosis. In fact, the expression of eEF1A is up-regulated by p53 transcription factor with the appearance in an erytroleukemic cell line of an apoptotic phenotype which expressed only the temperature-sensitive mutant p53 gene (1-2-3). These cells showed an overexpression of eEF1A when they were cultured at 32°C, with a tubulin morphology and localization similar to that one observed in cells treated with vincristine. Therefore, the microtubule-severing associated with the up-regulation of eEF1A by p53 may be a cause of the cell death (Kato et al., 1997; Kato, 1999). Recently, it has been shown that eEF1A is implicated in oxidative stress-induced apoptosis. In fact, in a cardiomyocites cell line, eEF1A levels undergo a rapid increase upon treatment with hydrogen peroxide, suggesting that the up-regulation of eEF1A plays an important role in execution of the apoptotic program in response to an oxidative stress (Duttaroy et al., 1998; Chen et al., 2000). Two isoforms of the protein are known, eEF1A1 and eEF1A2, that are encoded by two different genes and are expressed in a tissue specific manner (Lee et al., 1992, 1993a, b, 1994; Knudsen et al., 1993). In details, it has been shown that the eEF1A2 form plays a role in the protection of apoptosis mediated by caspase 3 (Ruest et al., 2002).

eEF1A and the ubiquitin mediated protein degradation

The degradation of cellular proteins through ubiquitin mediated pathway is initiated by the covalent attachment to the protein substrate of multiple ubiquitin molecules. This event leads to the subsequent delivery of the protein target to a macromolecular complex, the proteosome, which determines the proteolysis and degradation of the protein (Adams, 2003). It has been demonstrated that eEF1A is required for the degradation of N^{α}-acetylated proteins. The mechanism of action of eEF1A in the degradation process is not clear. However, several hypothesis have been made to explain the involvement of eEF1A in both protein synthesis and protein degradation processes. In the latter case, eEF1A may act as a ubiquitin C-terminal hydrolase, thus rendering the substrate more easily degraded by the 26S protease, or may play a chaperonin-like role, by inducing a correct folding of the protein/ubiquitins complex for the subsequent proteolitic degradation (Gonen et al., 1994, 1996). The availability of eEF1A in these process is depending upon cell conditions. During protein synthesis, eEF1A is associated in the formation of the ternary complex eEF1A · GTP · aa-tRNA whereas, during cellular stress, the reduction in the aa-tRNA levels will render eEF1A available for protein degradation. However, the molar ratio of eEF1A to aa-tRNA in eukaryotic cell varies from 1:6 (Slobin, 1980) to 1:1.5 (Edmond et al., 1996) and its concentration is quite low compared to the levels of the protein which is tightly bound to actin (Dharmawardhane et al., 1991; Edmonds et al., 1996). Since two F-actin binding domain on eEF1A have

Table 1. Post-translational modifications in mammalian EF1A

Source	Modification	Biological effect	Reference
Rabbit reticulocytes	Phosphorylation	Stimulation of enzyme activity	Venema et al., 1991
Rabbit reticulocytes	Phosphorylation	Increase in the exchange rate of GDP by GTP	Peters et al., 1995
Mouse 3T3-L1 cells	Phosphorylation	Insuline stimulated translational activity	Chang and Traugh, 1998
Rat liver	Phosphorylation	Reduction *in vitro* of the ability to bind F-actin	Izawa et al., 2000
Rabbit reticulocytes	Methylation (lysine) Addition of glyceryl-phosphorylethanolamine (glutamic acid)	Not reported	Dever et al., 1989
Mouse 3T3B cells	Methylation	Associated to SV40 transformation	Coppard et al., 1983

been identified with different pH sensitivity (domain I and III) (Liu et al., 1996), it might be possible that the involvement of eEF1A in the ubiquitination process could depend upon a pH-dependent release of the protein from the cytoskeleton triggered by cell stimulation (Dharmawardhane et al., 1991; Edmonds et al., 1996). At this regard, we analysed the involvement of eEF1A in the ubiquitination process during signal transduction. Preliminary immunoprecipitation experiments showed that in interferon-α induced apoptosis of human epidermoid cell line H1355 (Caraglia et al., 1999), there is an increase in the levels of eEF1A at short term exposure to the cytokine treatment with respect to untreated cells whereas, the amount of ubiquitin associated-eEF1A is initially low and increases as the levels of the protein returns to normal. Inhibition of the proteosome activity in H1355 cells showed an accumulation of ubiquinated eEF1A in cells treated with lactacystin or with both lactacystin and IFNα (Arcari et al., unpublished results). These results seem to be in favour of the involvement of eEF1A in the ubiquitin mediated protein degradation although the possible degradation of eEF1A itself through this mechanism during apoptosis cannot be excluded.

eEF1A and post-translational modifications

Post-translational modifications of protein play a role in the regulation of cell metabolism. The most frequent modification in the regulation of a variety of cell signalling and metabolic reactions is the phosphorylation and dephosphorylation reaction mediated by ATP and specific kinases and phosphatases. An other less frequent post-translational modification of proteins is the methylation, catalysed by methyltransferases using S-adenosylmethionine as methyl donor (Ado-Met) (Clark, 1993). Also in the case of eEF1A, several post-translational modification have been reported in association to a regulatory property of the factor. Table 1 summarizes the most important modification found in mammalian EF1A. These modifications have been found also in yeast (Zobel-Thropp et al., 2000), *Artemia salina* (Amons et al., 1983), *Mucor racemosus* (Sherman and Sypherd, 1989), EF-Tu from *E. coli* (Kral et al., 1999) and in several plants (Ransom et al., 1998). The role of eEF1A methylations has not been clarified however, they generally seems to increase of the activity of the factor.

Future perspective

Because the translation process plays a key role in the regulation of cell growth, the elucidation of the mechanisms by which eEF1A directly or indirectly regulate the cell growth and cell transformation could be of great help in order to better understand the cell de-regulation process during neoplastic transformation. In particular, the characterization of post-translational modifications of eEF1A associated to cell transformation or apoptosis, could give new insights for new anti-cancer terapeutic strategies.

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