Amino Acids (2012) 42:679–684
DOI 10.1007/s00726-011-1042-8

MINIREVIEW ARTICLE

Translational control of eIF5A in various diseases

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Received: 11 March 2011 / Accepted: 10 May 2011 / Published online: 5 August 2011

Abstract Translational control is a crucial component in the development and progression of different diseases. Translational control may involve selective translation of specific mRNAs, which promote cell proliferation or lead to alterations in translation factor levels and activities. Eukaryotic initiation factor 5A (eIF5A) is the only known protein to contain the unusual amino acid hypusine [N^{ε}- (4-amino-2-hydroxybutyl)-lysine], which is formed from the polyamine spermidine by two catalytic steps. eIF5A is involved in translation, elongation and stimulating peptide bond formation. Hypusination of eIF5A is essential for its activity in promoting cell proliferation. Meanwhile, there is evidence that eIF5A is a key protein in the pathogenicity of different diseases, such as diabetes, several human cancers, malaria and HIV-1 infections. Hitherto, the available data suggest that eIF5A has a role of a cell context-dependent function being more proliferative in the case of several human cancers and being involved under stress conditions in diabetes. Secondly, in HIV-1 infections and in diabetes, eIF5A also has a nuclear function by its sequence-specific binding of mRNAs as an mRNA-shuttle in conjunction with nuclear membrane export proteins. This binding may also influence the half-lives of mRNAs or their sequestration. Based on these data, there is a considerable therapeutic interest in eIF5A as a selective target for drug development through inhibition of hypusination.

Keywords eIF5A · Cancer · Diabetes · Malaria · HIV · Hypusine · Translation

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Abbreviations

2D-electophoresis	Two dimensional electrophoresis
MALDI-TOF	Matrix-assisted laser desorption ionization-time-of-flight
iNos	Inducible nitric oxide synthase
IL-1β	Interleukin-1β
TNF-α	Tumor necrosis factor α
IFN-γ	Interferon gamma
GTP	Guanosine triphosphate
GDP	Guanosine diphosphate
PKR	Protein kinase R
PERK	Proline-rich extensin-like receptor protein kinase
GCN2	General control nonrepressed 2 serine/threonine-protein kinase
Th1-type-cells	T-helper cells signal 1
Th2-type-cells	T-helper cells signal 2

Translation initiation: a brief insight

Translation of most mRNAs is controlled at the rate-limiting step of initiation (Silvera et al. 2010). The initiation phase leads to the assembly of an 80S initiation complex, consisting of 40S and 60S subunits, with bound methionyl tRNA and mRNA ready for initiation of the first peptide bond synthesis. A number of initiation factors facilitate the formation of the initation complex. Eukaryotic initiation factor 5A (eIF5A) is known to stimulate the synthesis of the first peptide bond and may also enhance translation elongation (Saini et al. 2009; Gregio et al. 2009) (Fig. 1).

In a first step, the 43S pre-initiation complex is formed. This complex consists of the 40S small ribosomal subunit, the initiating methionyl tRNA (Met-tRNA) and a group of

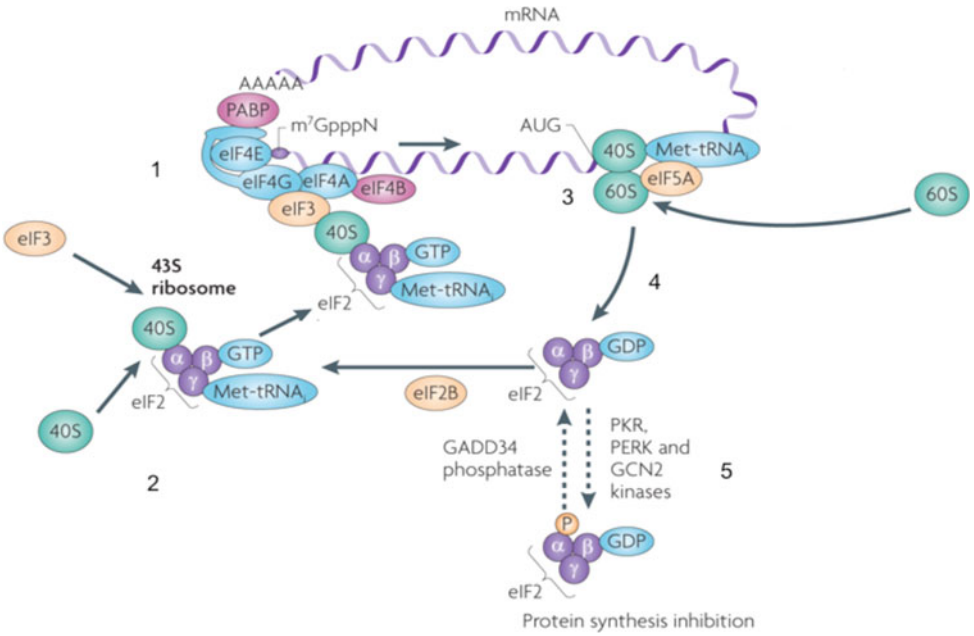

Fig. 1 The role of eukaryotic initiation factors (eIFs) in cap-dependent mRNA translation. *1* The eukaryotic initiation factor eI4F cap-initiation complex (eIF4G, eIF4E and eIF4A) assembles on the m7GpppNcap and interacts with the polyA tail binding protein (PABP) at the 3′ polyadenylated end of the mRNA. *2* The 40S ribosome subunit binds additional initiation factors like eIF3 and the ternary complex (eIF2-GTP-Met-tRNA) forming the 43S pre-initiation complex. *3* Subsequently the cap-initiation complex scans the mRNA from the 5′ end for the first initiation codon AUG. The 80S ribosome is left at the initiation codon to start protein synthesis. eIF5 stimulates peptide formation and translation elongation. *4* AUG recognition activates hydrolysis of GTP which is bound to eIF2 which consists of α, β and γ-subunits. This results in recruitment of the 60S ribosome and release of eIF2-GDP. The eIF-2 GDP is recycled to active eIF2-GTP to allow another round of translation initiation. Phosphorylation of eIF2α by the protein kinases PKR, PERK and GCN2 blocks GDP recycling mechanism on eIF2 and impairs protein biosynthesis. This can be reversed by GADD34 phosphatase

eukaryotic initiation factors (eIFs), including eIF2. Next, the 43S pre-initiation complex is recruited to the 5′ end of the mRNA, marked by an inverted m7GpppN cap. Association of the 43S pre-initiation complex with the cap is mediated by the cap-binding complex eIF4F, which consists of eIF4E, eIF4G and eIF4A. Associated with eIF4F and involved in initiation, are several other initiation factors, including the multisubunit complex eIF3, and mRNA binding proteins such as the polyA tail binding protein (PABP).

eIF5A promotes translation elongation

eIF5A is a small, acidic protein which is highly conserved in archae and eukaryotes (Wolff et al. 2007). The post-translational modification of eIF5A by hypusination strictly requires two sequential steps of enzymatic catalysis by deoxyhypusine synthase (DHS) and deoxyhypusine hydroxylase (DOHH). DHS transfers the aminobutyl moiety from spermidine to the ε amino group of a specific lysine residue in the eIF5A precursor protein, while DOHH completes hydroxylation to its active functional form (Park et al. 2010).

One of the major functions of polyamines in translation is that they are bound to RNA (Igarashi and Kashiwagi 2010) to enhance the translation rate of mRNAs. The polyamine spermidine is also required for the activation and posttranslational modification of eIF5A to its hypusinated form. Over the recent years there has been a shift in paradigm on the role of eIF5A in translation. First, eIF5A was identified as a translation initiation factor (Kemper et al. 1976) but recent results showed that eIF5A binds only to translating ribosomes (Zanelli et al. 2006; Zanelli and Valentini 2007). Moreover, polysome profiles suggest a block in translation elongation (Gregio et al. 2009; Saini et al. 2009) of eIF5A mutants and the profile was similar to that of wild type cells blocked at elongation by treatment with sordarin, an inhibitor of elongation factor 2 (eEF2) (Saini et al. 2009). In addition, a yeast temperature sensitive *eif5A* mutant was sensitive to sordarin like the *eif2* mutant. Taken together, these results suggested that eIF5A functionally interacts with eEF2 in the ribosome elongation cycle (Saini et al. 2009).

Is there a translational control of eIF5A in cancer cells?

Over the recent years, it has been shown that eIF5A proteins are overexpressed in human cancer cells. While the eIF-5A-1 isoform is constitutively expressed, the

expression of eIF52-isoform is normally extremely low, but is significantly upregulated in mouse embryonic livers and human hepatocellular carcinoma (HCC) cell lines (Lee et al. 2010).

Hitherto, it remains unclear how eIF5A overexpression of either isoforms in tumor cells promotes cell proliferation. In particular, eIF5A-2 is necessary for proliferation of those cancer cells lacking a putative tumor suppressor, exportin 4 (XPO4) (Zender et al. 2008). This suppressor protein is responsible for the nuclear export of both isoforms, i.e., eIF-5A1 and eIF-5A2 (Zender et al. 2008). However, it remains unknown how this suppressor is linked to translation and cell proliferation. Different studies suggested that eIF5A promotes cell proliferation by facilitating translation of specific, growth-promoting mRNAs, which support DNA replication and hyperproliferation of tumor cells (Hanauske-Abel et al.1995). For instance, identification of distinctive protein expression patterns in colorectal carcinoma detected eIF5A-1 as one of the four upregulated proteins (Lam et al. 2010) by 2D-electrophoresis and subsequent MALDI-TOF-TOF-MS depending on the abundance of the growth-promoting transcript. Alternatively, eIF5A might indirectly stimulate cell proliferation. Experiments in the past showed that hypusinated eIF5A-1 was involved in aberrant growth stimulation in intraepithelial neoplasia of the vulva (Cracchiolo et al. 2004), which is a precursor form of cancer.

Based on these results, there is a considerable therapeutic interest in eIF5A as a selective target through inhibition of hypusination. This notion is supported by previous results with imatinib, a drug which inhibts BCR–ABL tyrosine kinase and is administered in the treatment of chronic myeloid leukemia (CML) (Balabanov et al. 2007). Moreover, it was shown that imatinib down-regulates hypusination of eIF5A. Co-treatment with hypusination inhibitors (HI), i.e., ciclopirox or *N*-1-guanyl-1,7-diaminoheptane (GC7) caused an additive effect. These results might be attributed to a therapeutic interference of imatinib with signaling pathways downstream of the BCR–ABL tyrosine kinase to down-regulate eIF5A translation. Furthermore, hypusination inhibitors like GC7, an inhibitor of DHS and ciclopiroxolamine, which inhibits DOHH, exert an additive effect by blocking hypusination and thus formation of the active form of eIF5A.

eIF5A as a new target for therapy in the treatment of diabetes

Diabetes mellitus (Wild et al. 2004) is a condition in which the pancreas no longer produces enough insulin, or cells stop responding to the insulin that is produced, so that the glucose in the blood cannot be absorbed into the cells of the body. It is characterized by the dysregulation of blood glucose homeostasis. As of 2000, at least 171 million people worldwide suffer from diabetes, mostly in industrial countries. The main causes are overweight and obesity. There are two forms of diabetes: type 1 diabetes, which results from the degeneration of β cells to produce insulin and type 2 diabetes which is caused by the insulin resistance of β cells. In case of diabetes type 1 (TID1), insulin is the only drug for treatment, while type2 (TID2) diabetes can be treated with oral antidiabetics.

Although the two types of diabetes are different, they share a common mechanism of pathogenesis in which the β cells are destroyed by pro-inflammatory cytokines, i.e., IL-1β, TNF-α and IFN-γ. Upon exposure to antigens, islet-resident antigen presenting cells express cell surface-markers CD80, and CD83 which are required for T-cell activation. $CD4^+$ T cells release pro-inflammatory cytokines and TNF-α (Mathis et al. 2001) which induce necrotic and apoptotic pathways. Subsequently the pro-inflammatory cytokines lead to the activation of the Nos2 gene which encodes the inducible nitric oxide synthase (iNos) (Fig. 2a). The iNos enzyme is responsible for the production of nitric oxide, which leads to diminished ATP production and to cellular necrosis. Recent experiments by Maier et al. (2010a, b) suggest that the translation of the *Nos2* transcript is regulated by eIF5A. Moreover, eIF5A depletion as well as the inhibition of hypusination protects against glucose intolerance in inflammatory mouse models of diabetes. A knockdown of eIF5A in mice prevents hyperglycemia and leads to impaired translation of iNos mRNA (Maier et al. 2010a, b). Taken together, these experiments show that hypusinated eIF5A is required in part for nuclear export of iNos-encoding mRNA, which involves the export protein exportin1 (Fig. 2b). These results identify hypusinated eIF5A as an important target in preventing inflammatory processes damaging islet β cells (Evans-Molina et al. 2009).

The role of hypusinated eIF5A in *Plasmodium*

Malaria still remains a major problem of public health. Although accomplishments and progress has been made in the field of therapeutic intervention during the last years, there are approximately 3.2 billion people living in endemic areas with 225 million cases of clinical malaria and 781,000 malaria-related deaths (Alonso et al. 2011). One of the major changes in the recent paradigm of new antimalarials is the shift from malaria control to complete eradication of all five pathogenic human malarial parasites by preventing parasite transmission. To discover such a drug would be a long way, but the development of drugs which meet some of these requirements, i.e., mass

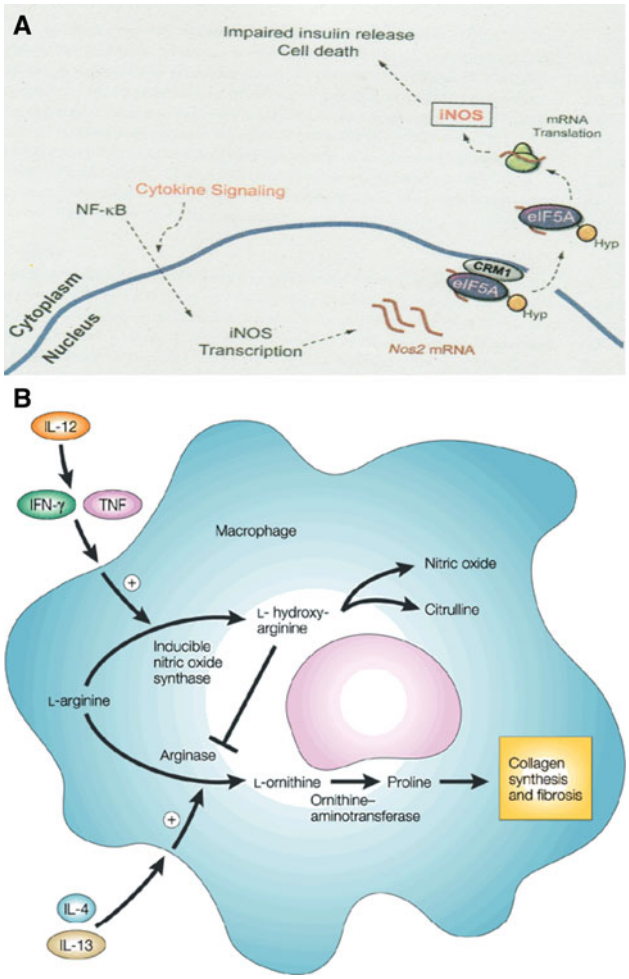

Fig. 2 A simplified proposed model for the role of eIF5A in diabetes. **a** eIF5A controls *Nos2* mRNA translation. Upon cytokine signaling, NF-κB migrates from the cytosol to activate transcription of the *Nos2* gene (nitric oxide synthase 2 gene). *Nos2* transcripts are transported out of the nucleus by the CRM1 transport protein and hypusinated eIF5A to the ribosomes where translaton occurs to form iNos (inducible nitric oxide synthase). iNos leads to ATP suppression and to inhibition of insulin release. Immune responses to pathogens in macrophages of mice (taken from "J Clin Invest. 2010, 120(6): 2156–2170"). **b** Th1-type (T helper cells signal1) 1(cytokines such as IFN-γ, IL-12 and TNF drive iNos expression in murine cells. Arginase breaks down arginine to produce urea and ornithine, which then can be metabolised further to proline as a possible source of energy and a building block for protein synthesis, polyamines and nucleotide biosynthesis. iNos competes with arginase for the same substrate, arginine. But unlike arginase, iNos produces citrulline and the radical NO which is not further metabolised. The Th2-type (T helper cells signal2) cytokines such as IL-4 induce arginase (taken from "http://www.nature.com/nri/journal/v2/n7/full/nri843.html")

administration or a single infrequent encounter, might contribute to the goal of eradication. This complete rethinking in the therapy and prophylaxis of malaria enforces new strategies in the process of drug target discovery. Novel approaches should focus on targets which are not only present in the asexual erythrocytic stages, but in the gamteocytic stages of the blood and in the sexual development of the parasite in the mosquito.

In view of all these requirements for novel chemotherapies in the treatment of malaria in the future, we have investigated the posttranslational modification of eIF5A in different *Plasmodium* species over recent years (Kaiser 2009).

The eIF5A protein from the benign malarial parasite *P.vivax* causing tertiary malaria, has been recently identified as a protein of 162 amino acids with a calculated molecular weight of 17.49 kDa and a theoretical pI of 5.41 (Kaiser et al. 2007). eIF5A from *Plasmodium vivax* shares 97% amino acid identity to its homolog from *P. falciparum* str. 3D7 (Molitor et al. 2004). Although both proteins are not located in the apicoplast genome, they share a high degree of homology to their plant homologs, i.e, *Arabidopsis thaliana* (61%) and *Nicotiana plumbaginifolia* (59%).

In the past, many experiments have shown that hypusination of eIF5A is essential for the growth of *Plasmodium.* A recent proteomic approach showed that inhibition of S-adenosyl-methionine-decarboxylase (Ado-MetDC), a key enzyme in the biosynthesis of spermidine, by the inhibitor CGP 48664A, known as SAM486A, resulted in a downstream effect on hypusine biosynthesis and depletion of hypusinated eIF5A (Blavid et al. 2010). Experiments based on reverse transcription have shown that *eif5A* transcripts occur in all erythrocytic stages of parasitic development (Kaiser et al. 2007) and maybe in gametocytes in blood stages, which has not been tested so far.

Hitherto, the functional role of eIF5A in *Plasmodium* remains unknown. In the near future, in vivo gene silencing of *eif5A* by RNA interference (RNAi) might probably provide more information. In the first in vitro approach among 18 tested siRNA constructs, only one construct, which targets the *eif5A* gene at nucleotide positions 163–184 was successful to achieve a silencing effect of the gene to approximately 30%.

Recent experiments performed by molecular genetics suggest that RNAi is not functional in malaria parasites (Baum et al. 2010). The authors showed that the expression of the analyzed proteins in *P.falciparum* and *P.berghei* by a variety of RNAi-based strategies was non-essential to either growth or development. Additionally, the authors undertook a comparative analysis of available apicomplexan and other protozoan genomes in an attempt to determine whether a primitive RNAi machinery exists in Apicomplexa. Taken together, these in silico data argued that RNAi is absent in malaria parasites. In contrast, there were several reports describing the successful use of RNAi for gene silencing in erythrocytic stages of *Plasmodium*, i.e., MybB1, a transcription factor necessary in the erythrocytic stages (Gissot et al. 2005). Kumar et al. (2002)

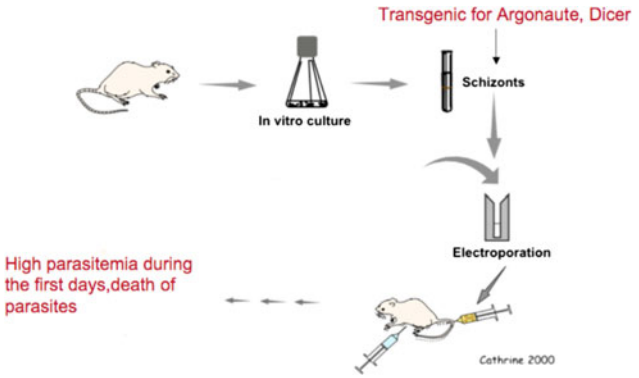

Fig. 3 A first approach to study RNAi in *Plasmodium*. Transgenic schizonts from *P. berghei* infected mice harboring the enzymes argonaute and dicer, were transfected with a siRNA construct of eIF5A from *P. vivax* by electroporation. In the subsequent step, the schizonts were used to infect mice. After two days of high parasitemia, parasites were eradicated

showed the requirement of a serine/threonine phosphatase for DNA replication in *Plasmodium*. Tuteja et al. (2008) identified a signal peptidase that is required for intra-erythrocytic growth by RNAi. Apart from electroporation (McRobert and McConkey 2002) siRNAs have been added to the culture medium. Cysteine proteases falcipain-1 and falcipain-2, which are necessary for hemoglobin degradation, have been shown to be essential for the blood stages (Dasaradhi et al. 2005).

With respect to the controversy whether a divergent RNAi machinery exists in *Plasmodium*, a first in vivo approach was initiated to knock-down *eif5A* in schizonts, which were transgenic for the enzymes argonaute and dicer (Fig. 3). These transgenic schizonts were capable of performing a primitive RNAi machinery. Preliminary results showed that after transfection of the *eif5a* construct into these transgenic schizonts, no eIF5A cDNA could be detected by reverse transcription. Moreover, when these schizonts were used for an infection in rodents, parasitemia decreased within a couple of days and the infection stopped.

Given the immense public health costs for malaria disease and the need for new drug targets, a silencing approach such as RNAi would be extremely beneficial. Moreover, the ability to use RNAi to silence gene expression in *Plasmodium* would provide a powerful means to gain insight into pathogenic blood stages.

eIF5A in HIV-1 infection

Highly active anti-retroviral therapy (HAART) has been shown to profoundly improve the morbidity and mortality among HIV-1-infected patients (Palella et al. 1998). HAART targets mainly three different viral proteins, i.e., reverse transcriptase (RT), protease and gp41 (Dybul et al. 2002). However, long-term administration of HAART resulted in significant adverse side effects including mitochondrial toxicity, lipodystrophy, diabetes mellitus, kidney diseases and osteoporosis for the patients. Alternatively, a continuing HAART therapy can lead to target resistance. Therefore, it is an important issue to discover new drugs and drug targets.

The replication of HIV-1 depends on the action of the viral Rev protein (Pollard and Malim 1998). eIF5A is a cellular cofactor of Rev (Bevec et al. 1996). Hofmann et al. (2001) showed that Rev constantly shuttles between the nucleus and the cytoplasm of host cells and primarily mediates the nucleocytoplasmic transport of incompletely spliced and unspliced viral mRNAs. These data suggest that eIF5A is involved in the metabolism of specific mRNAs.

Blocking eIF5A hypusination by DHS inhibition with the low molecular-weight compound CNI1493, a synthetic guanylhydrazone (Hauber et al. 2005), resulted in pronounced inhibition of replication of even in a series of multidrug-resistant viruses. Similar results were obtained by blocking DHS by RNAi.

The function of eIF5A in HIV-1 replication resemble that in diabetes, promoting the export and translation of the *iNos2* mRNA, just revisiting an old acquaintance (Hauber 2010).

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