Molecular & Biochemical Parasitology 187 (2013) 21–31

Contents lists available at SciVerse ScienceDirect

Molecular & Biochemical Parasitology

Review

Unique posttranslational modifications in eukaryotic translation factors and their roles in protozoan parasite viability and pathogenesis

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ARTICLE INFO

Article history:
Received 5 July 2012
Received in revised form 4 November 2012
Accepted 5 November 2012
Available online 28 November 2012

Keywords:
Eukaryotic elongation factor 1A
Eukaryotic initiation factor 5A
Eukaryotic elongation factor 2
Ethanolamine phosphoglycerol
Hypusine
Diphthamide
Protozoan parasites

ABSTRACT

Protozoan parasites are one of the major causes of diseases worldwide. The vector transmitted parasites exhibit complex life cycles involving interactions between humans, protozoa, and arthropods. In order to adapt themselves to the changing microenvironments, they have to undergo complex morphological and metabolic changes. These changes can be brought about by expressing a new pool of proteins in the cell or by modifying the existing repertoire of proteins via posttranslational modifications (PTMs). PTMs involve covalent modification and processing of proteins thereby modulating their functions. Some of these changes may involve PTMs of parasite proteins to help the parasite survive within the host and the vector. Out of many PTMs known, three are unique since they occur only on single proteins: ethanolamine phosphoglycerol (EPG) glutamate, hypusine and diphthamide. These modifications occur on eukaryotic elongation factor 1A (eEF1A), eukaryotic initiation factor 5A (eIF5A) and eukaryotic elongation factor 2 (eEF2), respectively. Interestingly, the proteins carrying these unique modifications are all involved in the elongation steps of translation. Here we review these unique PTMs, which are well conserved in protozoan parasites, and discuss their roles in viability and pathogenesis of parasites. Characterization of these modifications and studying their roles in physiology as well as pathogenesis will provide new insights in parasite biology, which may also help in developing new therapeutic interventions.
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Abbreviations: eEF1A, eukaryotic elongation factor 1A; eIF5A, eukaryotic initiation factor 5A; eEF2, eukaryotic elongation factor 2; EPG, ethanolamine phosphoglycerol; DHS, deoxyhypusine synthase; DOHH, deoxyhypusine hydroxylase.

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0166-6851/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molbiopara.2012.11.001

1. Introduction

The genomic content of every organism is limited, yet the coding capacity, i.e. the corresponding proteome, is very diverse. A cell has two basic ways to diversify its proteome: first, at the transcriptional level via alternate splicing and trans-splicing of mRNAs and second, through posttranslational modifications (PTMs) of proteins. The regulation of gene expression in kinetoplastids takes place at multiple levels, such as trans-splicing, polyadenylation, mRNA stability, transcript elongation, RNA translation and protein stability. Transcription in trypanosomatids generates large polycistronic transcripts, which are processed to monocistronic mRNAs by polyadenylation and trans-splicing of a mini-exon, or splice-leader, to primary transcripts. As a result, regulation of gene expression in kinetoplastids takes place mainly at the post-transcriptional level.

PTMs refer to a broad array of covalent modifications and processing of proteins. These modifications can be reversible or irreversible. Reversible modifications include the specific attachment of small molecules, such as phosphate, acetate, ADP-ribose, AMP, methyl and hydroxyl groups to specific amino acid residues of a given protein. These modifications may not only affect the biochemical properties of proteins but also modulate their functions, localization, turnover and interactions with other macromolecules. Thus, PTMs increase the functional diversity of a given protein, thereby adding a layer of complexity to the proteome in eukaryotes and to a limited extent in prokaryotes [1,2].

Among many protein modifications known till date, three of them are exceptional as they occur only on single proteins: ethanolamine phosphoglycerol (EPG) glutamate, hypusine and diphthamide modifications of eukaryotic elongation factor 1A (eEF1A), eukaryotic initiation factor 5A (eIF5A) and eukaryotic elongation factor 2 (eEF2), respectively. Interestingly, all three proteins are involved in the elongation step of translation in eukaryotes [3]. Translation is a basic event required by the cell to make proteins. Therefore, homologs of translation factors involved in this process can be found in eukaryotes, archaea and bacteria. Translation involves three main steps: (i) initiation, (ii) elongation, and (iii) termination (Fig. 1). During initiation, a 43S pre-initiation complex is formed comprising of the 40S subunit, eIF2-GTP, Met-tRNAi, and eIF3. This is joined by cap binding complex of eIF4F and the factors eIF4A and eIF4B which further assist the complex in binding mRNA, thus forming the 48S complex. This complex associates with the 60S large ribosomal subunit to form the 80S ribosome [4], which has a mettRNA bound at its P site. The process starts with a cognate aminoacyl tRNA brought to the A site of the ribosome in form of a ternary complex with eEF1A and GTP. Following hydrolysis of the bound GTP to GDP, eEF1A is released, while the growing polypeptide is transferred from the P site tRNA to the aminoacyl tRNA at the A site. The peptidyl tRNA is then translocated from the A to the P site by GTP-bound eEF2, whereby eIF5A has been suggested to assist eEF2 in translocation. This cycle repeats until the ribosome reaches the stop codon where the process stalls, resulting in termination of elongation (Fig. 1).

The three translation factors eEF1A, eEF2 and eIF5A are phylogenetically well conserved [3]. The eukaryotic translation elongation factor complex consists of three or four subunits: eEF1A, eEF1B α, eEF1 β, eEF1B γ and eEF1B β. It is a GTP-binding complex, where GTP acts as a positive allosteric regulator of eEF1A [5]. The intrinsic GTPase activity of eEF1A is very low but is enhanced by

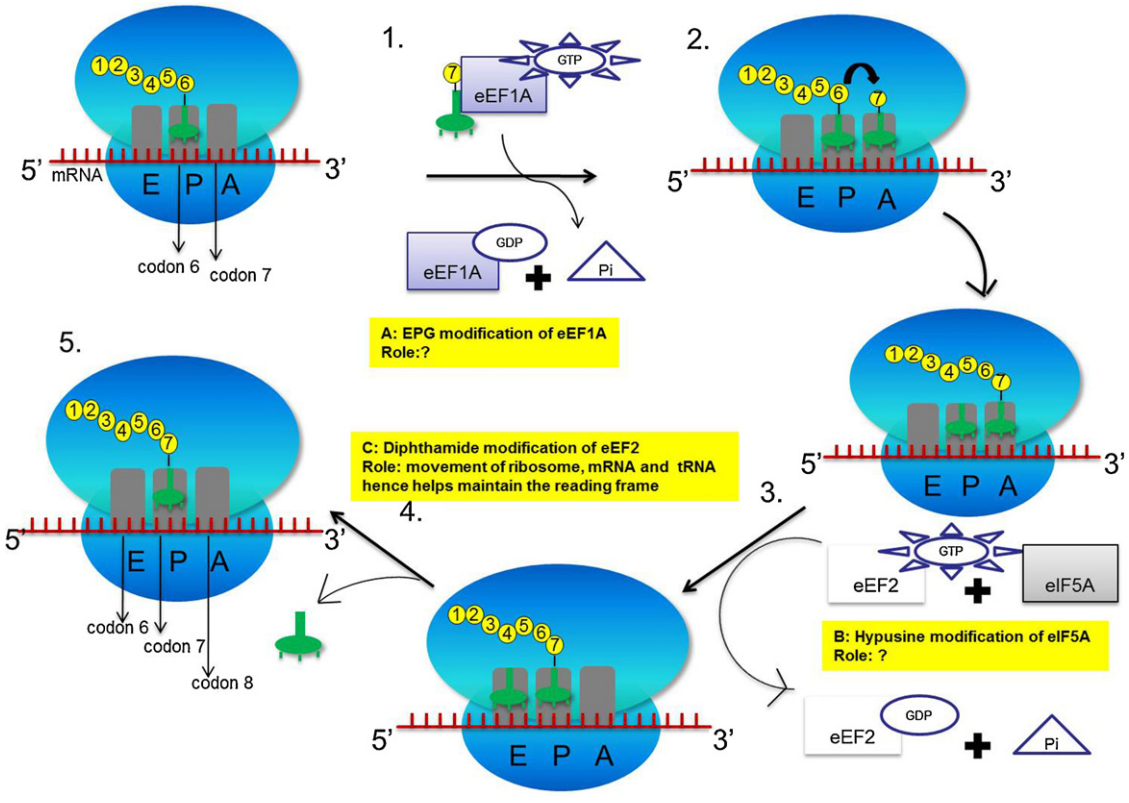

Fig. 1. Translation elongation cycle. (1) eEF1A along with GTP escorts specific aminoacyl tRNA (aa-tRNA) to the ribosome bound with mRNA at the interface of the two subunits and a peptidyl tRNA at the P site. Following GTP hydrolysis, the aa-tRNA is transferred to the A site of the large subunit. (2) Peptidyl transferase reaction transfers the growing polypeptide from peptidyl tRNA to aa-tRNA. (3) eEF2A bound to GTP assists in translocation of the ribosome, followed by GTP hydrolysis. eIF5A is supposed to assist eEF2A in this process. The peptidyl tRNA moves from A to P site. (4) Uncharged tRNA exits the ribosome from the E site. (5) Ribosome ready to start another cycle. Three post-translational modifications of elongation factors are: (A) EPG modification of eEF1A. (B) Hypusine modification of eIF5A. (C) Diphthamide modification of eEF2. Diphthamide is involved in maintaining the reading frame during translocation. The roles of hypusine and EPG in translation are not known.

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