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Mini-review

Eukaryotic translation initiation factors in cancer development and progression

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ABSTRACT

Eukaryotic gene expression is a complicated process primarily regulated at the levels of gene transcription and mRNA translation. The latter involves four main steps: initiation, elongation, termination and recycling. Translation regulation is primarily achieved during initiation which is orchestrated by 12 currently known eukaryotic initiation factors (eIFs). Here, we review the current state of eIF research and present a concise summary of the various eIF subunits. As eIFs turned out to be critically implicated in different oncogenic processes the various eIF members and their contribution to onset and progression of cancer are featured.

1. Introduction

1.1. eIFs and translation

Eukaryotic gene expression is a process mainly regulated at the levels of gene transcription and mRNA translation. Deregulation of translation (initiation, elongation, termination, recycling) results in abnormal gene expression, and thus leads to uncontrolled cell growth potentially resulting in cancer formation [1]. Within the four stages of translation, regulation is mainly achieved during initiation which is the rate limiting step in the translational cascade. Hence this highly critical phase of gene expression is of utmost interest for targeting cancer [1].

The classical process of translation initiation is also referred to as canonical translation initiation, in contrast to alternative ways like, e.g. IRES mediated translation initiation. The major players in canonical translation initiation are the eukaryotic translation initiation factors (eIFs), comprising eIF1, eIF1a, eIF2, eIF2b, eIF3, eIF4a, eIF4e, eIF4g, eIF4b, eIF4h, eIF5 and eIF5b (Table 1). The subunits eIF4a, eIF4e and eIF4g build the heterotrimeric complex eIF4F [2]. The canonical process is primed by formation of the 43S pre-initiation complex, to which mRNA is recruited together with the eIF4F complex and the poly(A) binding protein (PABP). The 43S pre-initiation complex consists of the small 40S ribosomal subunit, the initiating methionyl-tRNA bound to eIF2-GTP (eIF2-GTP-Met-$tRNA_i$ is also known as the ternary complex) and eIFs 1, 1a and 3. Subsequently, the mRNA is scanned for the first AUG in the 5′UTR until correct binding of tRNA anticodon loop to the initiator AUG on the mRNA assisted by eIF1. The scanning process is facilitated by eIF1 and eIF1a by altering the structure of the mRNA-binding cleft. This interaction enables functional 80S ribosome assembly on the mRNA and translation to take place [2].eIF3 is believed to function as a scaffold, interacting with other eIFs and the 40S ribosome. eIF3 also interacts with the eIF4F complex via eIF4g. The eIF4F complex fulfils a number of tasks in translation initiation, including the scanning process. eIF4e binds to mRNA's cap structure, eIF4a possesses helicase activity and is suggested to be positioned by eIF4g at the ribosomal mRNA entry channel. Encountering a perfect matching AUG start codon arrests the scanning PIC and hydrolyzes eIF2 in the ternary complex, followed by the release of eIF2 and other eIFs and subunit joining. In the final stage of translation initiation, eIF2 is in its inactive GDP bound state, GTP bound to eIF5B is hydrolyzed and the translation factor is disassociated from the ribosome. In contrast, eIF3 might stay on the ribosome for several reinitiation cycles [141]. Detailed roles of these and all other eIFs are highlighted in this review. Their involvement and interactions during translation initiation as well as their evolutionary conservation have been described previously [3–5]. All eIF subunits, including eIF6, a non-core eIF, and their function as understood today are listed in Table 1 (Table 1). A more detailed summary of these proteins, alongside detailed information concerning size and reference sequences, is given in Table 2 (Table 2).

As mentioned above, an altered translation initiation and therefore changed gene expression is increasing the risk of cancer devel-

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opment. Indeed, previous work showed that dysregulation of many eIFs is associated with malignant transformation and cancer progression [6–8]. Here we analyze which eIF subunits have been described in different tumor entities and if they were found to interact with known cancer related pathways. In the following we will discuss the various eIF members and stress their contribution to carcinogenesis.

2. Eukaryotic translation initiation factors in detail

2.1. Eukaryotic translation initiation factor 1 (eIF1)

Two protein factors to be discussed in this section are often confused with each other: eIF1 and eIF1a, the latter being formerly called eIF4C.eIF1 is a 113 amino acid (AA) long protein which is highly conserved from archaea and bacteria to humans [9]. In yeast, two different mutation classes were identified, denoted *sui1* and *mof2*. The human isoform resembles the *sui1* mutant, that in yeast allows initiation to take place upon AUG-mismatch base pairing in absence of an initiator tRNA [10]. eIF1a is a 144AA long protein encoded on chromosome X, therefore it is also called x-linked eIF1a or eIF1AX. Both proteins were reported to be essential for protein translation initiation [11].eIF1 as well as eIF1a are required for translation initiation and mRNA screening, during which a preformed initiation complex that binds the 5′-cap region is shifted to the first AUG initiation codon. Of notice, eIF1 that is of high importance for correct AUG recognition and binding, itself possesses an AUG in a structurally and sequence-wise complex context region [12]. eIF1a was reported to trigger the formation of the pre-initiation complex, together with eIF2, 3, 4a, 4b and 4F. Functions of eIF1 and eIF1a are distinct, however synergistic, as both are required for 48S complex assembly and binding at the initiation codon [12].

Human genotoxic and endoplasmic reticulum stress-inducible transcripts were previously described. A cDNA identified in this pool, termed A121, was found to encode for eIF1, indicating that genotoxic stress modulates translation initiation via this eIF [13]. The protein was shown to be non-uniformly distributed throughout different tissues, with higher levels in heart and skeletal muscle than in brain, placenta, lung, pancreas, liver and kidney, as analyzed by Northern blotting of various human tissue samples [13].

To prove the induction of eIF1 upon genotoxic stress signaling, CHO cells were treated with different agents, ranging from UV and UV mimetics over ionizing radiation to heat shock, and were analyzed under serum starvation [13]. Induction of A121/eIF1 was observed in cells treated with UV or UV mimetics and with base damaging agents [13]. This UV dependent effect could be reproduced in various human cancer cell lines [13]. Furthermore, the induction of eIF1 and therefore translation initiation was shown to occur in a p53 independent manner (Fig. 1) [13].

Not only the close evolutionary relation between yeast *sui1* mutant of eIF1 and the human homologue but also the structure and interactions of the translation initiation factors are similar [9]. Three of the yeast mutated residues are conserved in human eIF1: Asp88, Gln89 and Gly112. These three are in close proximity to the proteiń surface where they build a putative binding site for interaction partners. Clusters of positive charges on the surface of the respective protein were also indicative of putative RNA-binding. Still, this could not yet be confirmed *in vitro*[9].

The direct interaction between eIF1 and eIF5 was first detected in a yeast-two-hybrid system, but was considered as not fully proven and speculative until recently two interaction sites were identified using NMR spectroscopy [12,14]. The binding of eIF1 to eIF3c could be shown *in vitro*[15]. This interaction is suggested as critical for recruitment of eIF1 to the 40S ribosomal subunit by eIF3 in protein translation initiation. Little is known about eIF1 and eIF1a during carcinogenesis. Tyrosine phosphorylation of eIF1 was reported to occur in anaplastic large cell lymphpomas (karpas 299 and SU-DHL-1) during a profiling of tyrosine phosphorylation in various cancer cell lines [15]. eIF1a was identified as a binding partner of Nemo (IKKγ), suggesting a role of eIF1a in NF-κB signaling (Fig. 1) [16].

Both suggested interactions are not yet fully acceptedand were not described to affect eIF1's and eIF1a's translation initiation activity [15,16].

2.2. Eukaryotic translation initiation factor 2 (eIF2)

eIF2 is a heterotrimeric initiation factor consisting of the subunits eIF2α, β and γ, which together participate in eIF2–Met-tRNA$_i$–GTP complex formation.

This eIF2-GTP is hydrolyzed during translation initiation, yielding eIF2-GDP. The guanine nucleotide exchange factor of eIF2-GDP is eIF2B. eIF2B consists of five non-identical subunits, eIF2B1 to eIF2B5, and represents a distinct entity from eIF2 [21].

The α subunit of eIF2 (eIF2α) can be phosphorylated by four stress–responsive kinases, globally referred to as eIF2AKs, including double stranded RNA activated protein kinase (PKR) [17], general control non-repressed 2 (GCN2) kinase [18], heme-regulated inhibitor (HRI) [19] and PKR like endoplasmic reticulum kinase (PERK) [20] at Ser51.

Table 1
Function in translation initiation and important references to eIFs.

Protein	Function	Refs.
eIF1	Fidelity of start codon selection, recognition of optimal AUG context, prevents premature eIF5 binding which would activate downstream events	[53,123]
eIF1a	Fidelity of start codon selection, in cooperation with eIF1 promotes ribosomal scanning and initiation codon selection	[124,125]
eIF2	Binds initiator-Met-tRNA in a ternary complex and delivers it to the 40S ribosome	[126,127]
eIF2B	Guanine nucelotide exchange factor, activates eIF2, mutations are related to several leukodystrophies referred to as eIF2B-related disorders	[128,129]
eIF3	Consists of 13 subunits. Functional core: eIF3a, eIF3b, eIF3c, eIF3e, eIF3f, eIF3h. Main functions: binding of 40S ribosomal subunit, preventing premature binding of 60S, facilitates binding to the ternary complex and mRNA The full scope of action and distribution of roles to single subunits is only beginning to be elucidated	[5,32,130]
eIF4F	Multisubunit complex: eIF4a: RNA helicase, eIF4e: cap binding activity, eIF4g: scaffolding protein and interaction partner for other proteins, one of which is PABP. This interaction loops mRNA and is thought to be a checkpoint for translational control	[131,132]
eIF4b	RNA-binding protein that enhances the RNA helicase activity of eIF4F (eIF4a). It is a downstream target of mTOR kinase	[85,133]
eIF4h	Has sequence homolgy with eIF4b and also stimulates RNA helicase activity of eIF4F (eIF4a). Alternative splicing is associated with tumorigenesis. The EIF4H gene is deleted in the neuro developmental disorder called Williams sysndrome	[134,135]
eIF5	Interaction partner of eIF2, inhibits GDP dissociation and regulates recycling of inactive-GDP bound eIF2 after a completed round of translation initiation	[21,122,136]
eIF5b	GTPase, responsible for ribosomal subunit joining	[131]
eIF6	Binds to 60S ribosome and regulates ribosome biogenesis. a complete role in translation initiation is not defined to date	[113,115]

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