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Mini-review

eIF3a: A new anticancer drug target in the eIF family

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ABSTRACT

eIF3a is the largest subunit of eIF3, which is a key player in all steps of translation initiation. During the past years, eIF3a is recognized as a proto-oncogene, which is an important discovery in this field. It is widely reported to be correlated with cancer occurrence, metastasis, prognosis, and therapeutic response. Recently, the mechanisms of eIF3a action in the carcinogenesis are unveiled gradually. A number of cellular, physiological, and pathological processes involving eIF3a are identified. Most importantly, it is emerging as a new potential drug target in the eIF family, and some small molecule inhibitors are being developed. Thus, we perform a critical review of recent advances in understanding eIF3a physiological and pathological functions, with specific focus on its role in cancer and anticancer drug targets.

Introduction

Translation is one of the key steps of gene expression, with four major stages: initiation, elongation, termination, and ribosome recycling [1]. The initiation step is rate limiting and highly regulated [2]. In eukaryotes, the eukaryotic translation initiation factors (eIFs) are major players involved in this process with at least 12 members [3]. Among them, eIF3 is the largest and most complex factor, comprising 13 subunits designated from eIF3a to eIF3m [4]. As the largest subunit of eIF3, eIF3a is widely and extensively investigated. Great progress has recently been achieved on eIF3a, and it is emerging as a new potential anti-cancer drug target. In this review, we provide the latest vision of eIF3a structure, expression, and its role in cellular biological processes and cancers as well as evidence on eIF3a as a therapeutic target.

eIF3a structure, expression, and distribution

Human eIF3a is a 170-kDa protein consisting of 1382 amino acids. The *eIF3a* gene is located at 10q26, spanning a region of 46 kbpp DNA (Fig. 1A) [5–8]. It is a highly conserved gene with mutations mostly in the noncoding region. Fig. 1B summarizes the frequency of eIF3a somatic mutations in human cancers based on the analysis of the catalogue of somatic mutations in cancer (COSMIC) database. Mutation, amplification, and deletion of this gene has been detected, which mostly occur in solid tumors, but the functional significance of them needs to be clarified. However, a few germline mutations are reported to have functional consequences, including two intronic polymorphisms (rs3824830 and rs10787899) that are significantly associated with an altered risk of breast cancer [9]and two exonic polymorphisms (rs3740556 and rs77382849) that correlated with the response and toxicity of platinum-based chemotherapy in patients with non-small cell lung cancer (NSCLC) [10,11]. It is interesting to note that rs77382849 is a nonsynonymous single nucleotide polymorphism (SNP) located in exon 16 with amino acid change from Arg to Lys; recently, it has been observed to be associated with gastric cancer susceptibility [12]. However, how this mutation affects cancer susceptibility and drug responses remains elusive.

Recently, the high-resolution architecture of eIF3a protein in the context of eIF3 complex is visualized by a series of studies [13–20]. eIF3 is a large complex with 13 subunits and organized by two submodules: the proteasome-COP9-signalosome eIF3/Mpr1, Pad1 N-terminal (PCI/MPN) octamer core (a, c, e, f, h, l, k and m) and five peripheral (b, d, g, i, and j) subunits [21](Fig. 1). eIF3a has a long and extended structure to link both core and peripheral modules. There are three major domains of eIF3a protein: PCI, spectrin, and C-

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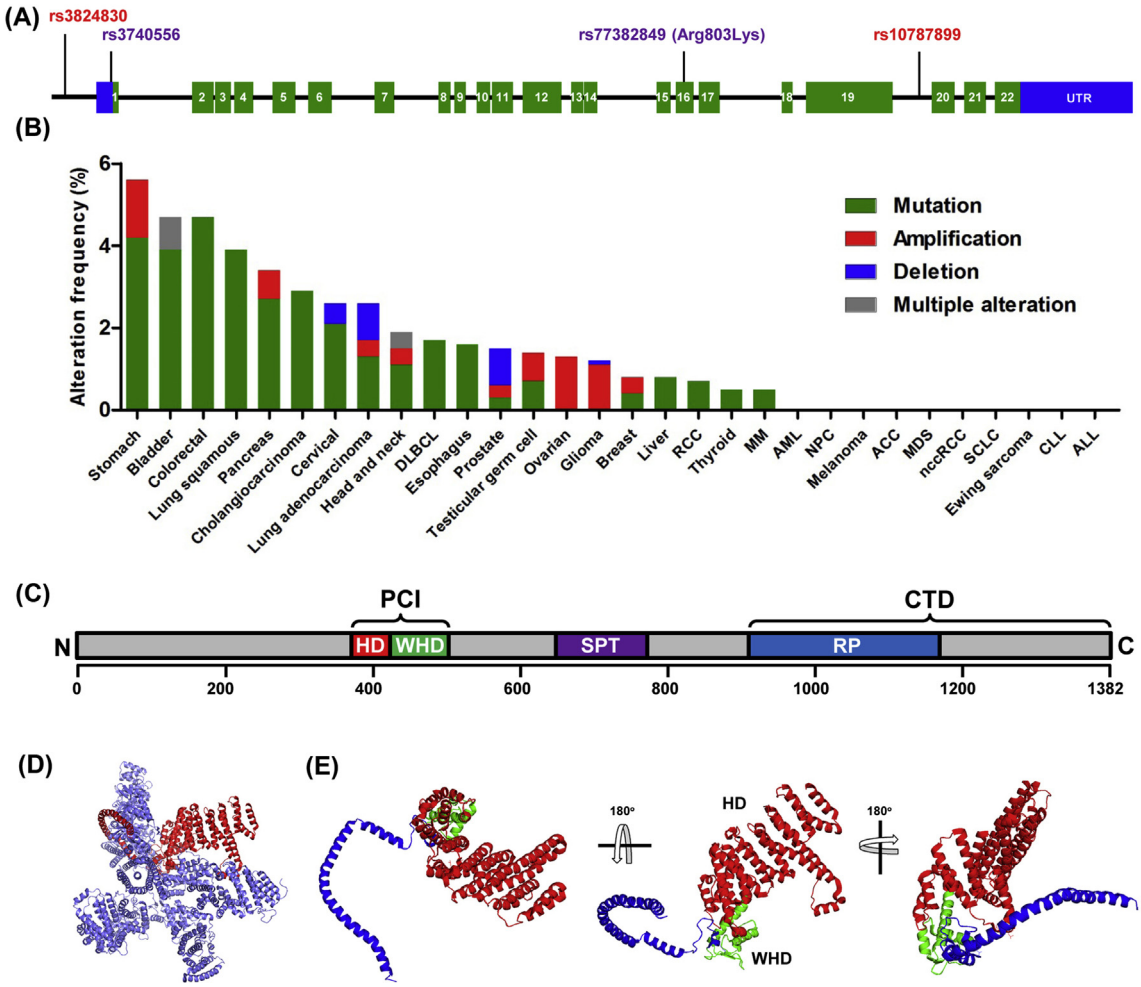

Fig. 1. The structure and genetic polymorphisms of eIF3a. (A) Genomic structure of eIF3a. The horizontal line represents its genomic entire length; exons and UTRs are indicated by green and blue boxes, respectively. The distribution of four SNPs with functional significance is indicated. Coding and noncoding region SNPs are indicated as purple and red, respectively. (B) The frequency of eIF3a somatic alterations in human cancers. The results are based on the analysis of catalogue of somatic mutations in cancer (COSMIC) database. (C) Schematic model of positions of eIF3a protein domains. (D) Structure of eIF3a in the context of eIF3 core subunits (a,c,e,h,k,l,m and f) (from des Georges et al. [18].). eIF3a is colored red. (E) Structure of eIF3a in different orientations, colored variably by domains. CTD: C-terminal domain, HD: helical domain, WHD: winged helix domain (From des Georges et al. [18].). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

terminal domain (CTD) [22]. The PCI domain is located in the N-terminus, which mainly contains an α-helix. This domain further contains an N-terminal helical domain (HD) and a C-terminal winged helix domain (WHD) [16,23]. eIF3a dimerizes with eIF3c, and WHDs of two PCI modules serve as the interface [15,18,24]. The second domain of eIF3a is the spectrin domain. The basic structure of this domain is three helices separated by two loop regions [25,26]. The exact function of this domain is still unknown, but it may also mediate the interaction of eIF3a with other proteins. It is reported that eIF3b and eIF3i concurrently bind to the spectrin domain, which serves as a docking site for the formation of eIF3a-b-i-g complex [27]. The largest domain of eIF3a is CTD, and it contains a subdomain (RP domain) with 10-amino acid repeat sequence. This sequence can be divided into about 25 repeats of DDDRGPRRGA [8]. The eIF3a CTD is a long helix bridging eIF3a with peripheral subunits. In mammals, at least three peripheral subunits (b, g, and i) are linked in a flexible manner to the core eIF3 module through the eIF3a CTD helical tail. In addition, it also mediates the binding of eIF3a with the 40S ribosome to facilitate mRNA recruitment and scanning [28–31].

In humans, eIF3a appears to be ubiquitously expressed in all tissues. Its expression profile during development is studied using a mouse model [32]. During fetal development, eIF3a is highly expressed in all tissues, including the liver, kidney, heart, lung, stomach, and intestine. Its expression is decreased during the postnatal stage and becomes undetectable in the kidney, stomach, and intestine. Consistently, eIF3a protein is also low and undetectable in normal adult human tissues of the liver, lung, colon, breast, kidney, and ovary [22]. However, eIF3a mRNA can be detected in all human tissues, especially with high levels in kidney, pancreas, skeletal muscle, and testes [22,33]. The reason for the inconsistency in detecting eIF3a mRNA and protein in tissues is unclear. It is possible that eIF3a expression may be regulated post-transcriptionally at the translational level. The subcellular distribution of eIF3a has also been reported, and is found to be located in plasma membranes, cytoplasm, and nuclei [33,34]. About 20% of eIF3a is associated with plasma and endoplasmic reticulum membranes, the remaining protein is located in the cytoplasm [34], and a small amount of eIF3a is detected in nucleus [33].

In summary, eIF3a is a highly conserved gene. Its protein has three major domains and adopts a long, extended structure with a CTD tail. The PCI domain interacts with core modules of eIF3 (especially eIF3c), while the spectin and CTD domains mediate interaction with peripheral eIF3 subunits. eIF3a is ubiquitously

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