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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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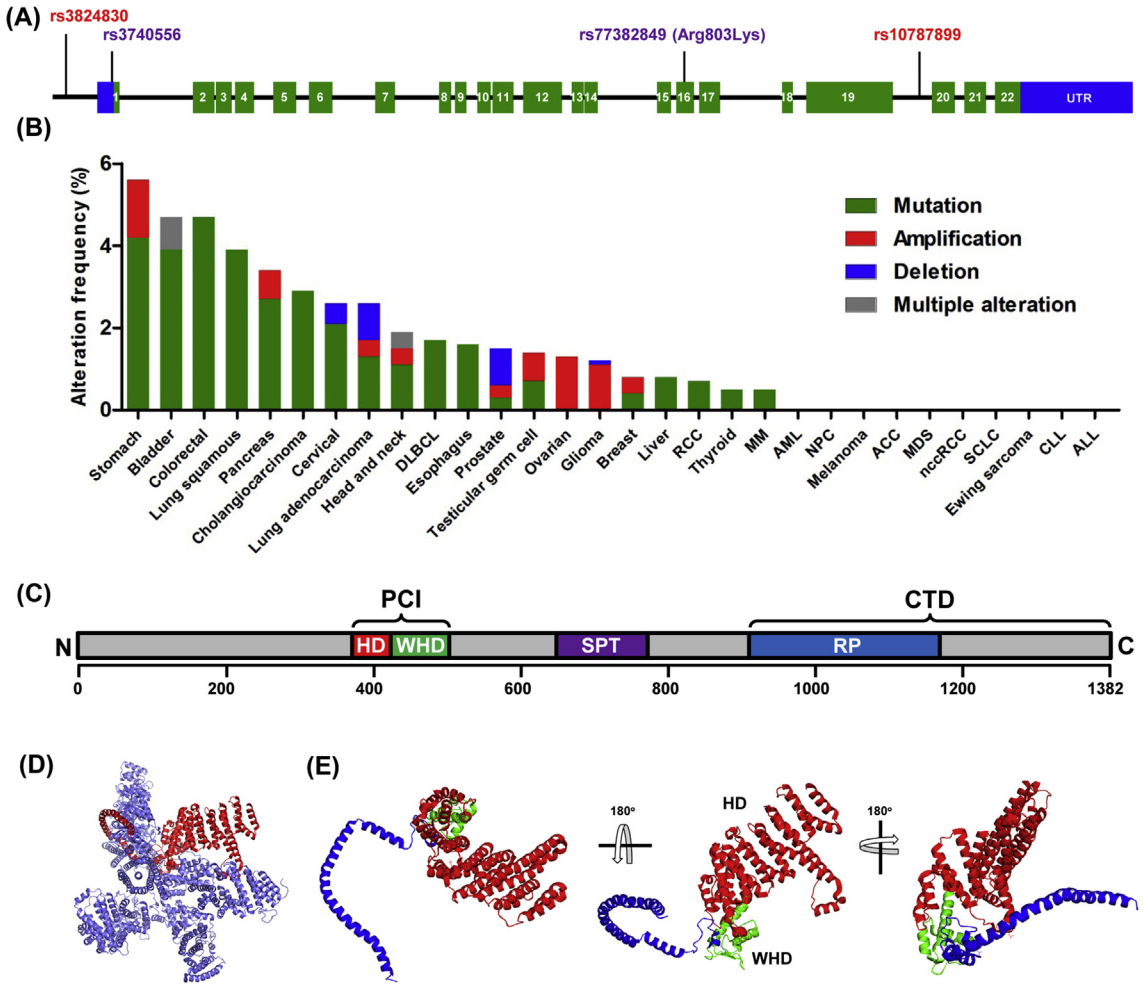

Fig. 1. The structure and genetic polymorphisms of eIF3a. (A) Genomic structure of eIF3a. The horizontal line represents its genomic entire length; exons and UTRs are indicated by green and blue boxes, respectively. The distribution of four SNPs with functional significance is indicated. Coding and noncoding 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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expressed in all tissues, and is mainly located in the cellular cytoplasm.

eIF3a mediated biological functions

Previously, eIF3a was thought to be just a translation initiation factor for mRNA translation [35]. Recent accumulating evidence suggests that eIF3a may have many regulatory functions in cellular, physiological, and pathological process (Fig. 2).

Cellular process

Translation initiation

As a translation initiation factor, the primary function of eIF3a is to participate in the formation of the eIF3 complex, and it contributes to the initiation steps in mRNA translation (Fig. 3). First, eIF3 binds to the 40S subunit ribosome to prevent its association with the 60S subunit [36,37]. By using cryoelectron microscopy, it is shown that eIF3 binds to the solvent exposed side of the 40S subunit [38]. The N-terminal domain binds to RPS0/S2 and CTD interacts with helices 16–18 of the 18s rRNA, RPS2/S5 and RPS3/S3 [29–31,39–41]. Second, eIF3 stimulates the formation of 43S PIC. Findings from an *in vitro* study suggest that eIF3 facilitates the binding of ternary complex (TC) to the 40S subunit [36,37,42]. Depletion of eIF3a reduces the binding capacity of 40S subunit with multifactor complex containing TC, eIF1 and eIF5, which is required for PIC formation [43]. Finally, eIF3 simulates the binding of 43S PIC with mRNA. *In vitro* studies have shown that eIF3 binds with mRNA directly, and it strongly promotes 43S PIC binding with long 5′UTR mRNAs [37,44,45]. On the other hand, eIF3 also interacts with eIF4G to form a bridge between 43S PIC and eIF4F/mRNA complex [46,47]. Translation can also be initiated by a cap-independent mechanism mediated by the internal ribosomal entry site (IRES) element in mRNAs. It recruits the 40S subunit directly to start translation without scanning from the 5′ end of mRNAs [48]. It has previously been shown that eIF3a together with eIF3c mediates hepatitis C virus IRES activity by directly binding to it [49–51]. We recently identified a new IRES element in the 5′ UTR of replication protein A2 (RPA2) and showed that eIF3a bound to this IRES element and inhibited its activity [52]. These studies together indicate that eIF3a is a key player in the process of both cap-dependent and cap-independent translation initiation.

Cell cycle

The involvement of eIF3a in cell cycle regulation was first reported in yeast [53]. In mammalian cells, eIF3a expression oscillates with the cell cycle and peaks in the S phase [54,55]. It also mediates the effect of some cell cycle modulators. Mimosine is a G1 cell cycle blocker, which is commonly used as a synchronizing agent for mammalian cells. It decreases eIF3a expression prior to G0/G1 cell cycle arrest [56]. Serum starvation induces G0/G1 arrest and nocodazole induces G2/M arrest, both of which are sensitized by eIF3a knockdown. In contrast, hydroxyurea-induced S phase arrest is desensitized by eIF3a knockdown. Although the detailed molecular mechanisms of eIF3a in cell cycle regulation remain unknown, it is thought that $p27^{kip1}$, a cyclin-dependent kinase (CDK) inhibitor that controls the cell cycle progression at G1 phase, is down-regulated by eIF3a and may mediate the function of eIF3a in mimosine-induced G1 arrest [56]. However, eIF3a upregulates the synthesis of ribonucleotide reductase M2 (RRM2), which is required for DNA synthesis in S phase. This regulatory function of eIF3a may be required for the S phase and, thus, eIF3a expression peaks during the S phase [57].

DNA synthesis and repair

DNA synthesis is an essential biological process of cells, and its regulation is important for controlling cell growth and proliferation. eIF3a was first observed to regulate DNA synthesis in H1299 cells, where reducing its expression using antisense cDNA decreases about 50% global DNA synthesis [57]. This effect is mediated by decreasing the synthesis of RRM2 protein, which controls the DNA synthesis rate-limiting step of converting ribonucleotides to their corresponding deoxyribonucleotides. However, another study unveils that knocking down eIF3a increases epidermal growth factor (EGF)-stimulated DNA synthesis [58]. eIF3a is reported to be a negative regulator in the EGF/extracellular signal-regulated kinase (ERK) pathway and inhibits EGF-induced ERK activation. It may negatively regulate the ERK pathway by binding with β-arrestin 2,

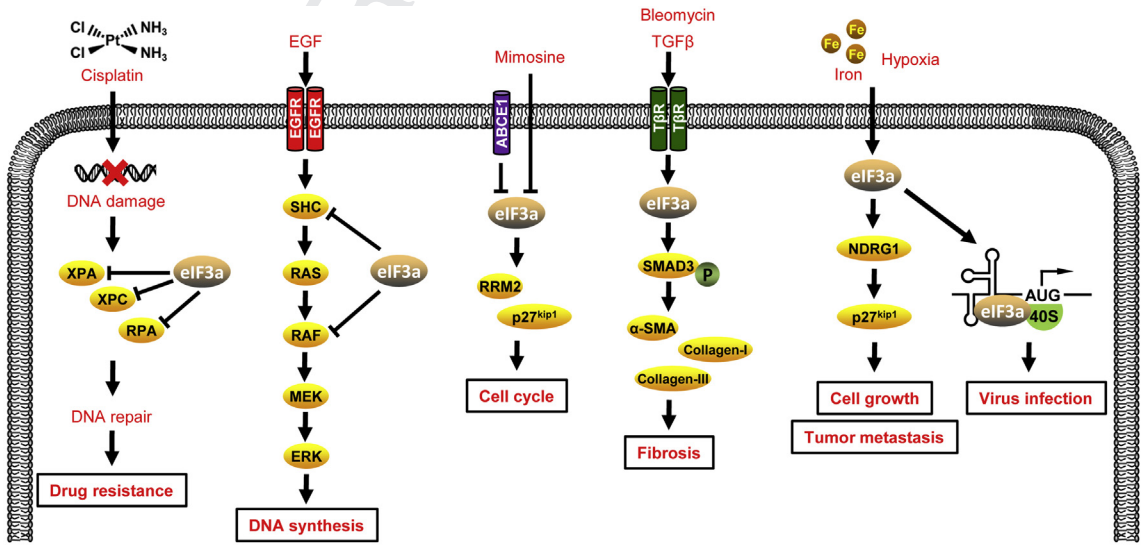

Fig. 2. A schematic overview of signaling pathways involving eIF3a and their corresponding biological function. The components in the pathways are indicated as self-explanatory symbols. XPA/C: xeroderma pigmentosum complementation group A/C, RPA: replication protein A, EGFR: epidermal growth factor receptor, ERK: extracellular signal-regulated kinase, RRM2: ribonucleotide reductase M2, TGFβ: transforming growth factor β, TβR: TGFβ receptor, SMAD3: mothers against decapentaplegic homolog 3, α-SMA: α-smooth muscle actin, NDRG1: N-myc downstream regulated gene-1. ABCE1: ATP binding cassette subfamily E member 1.

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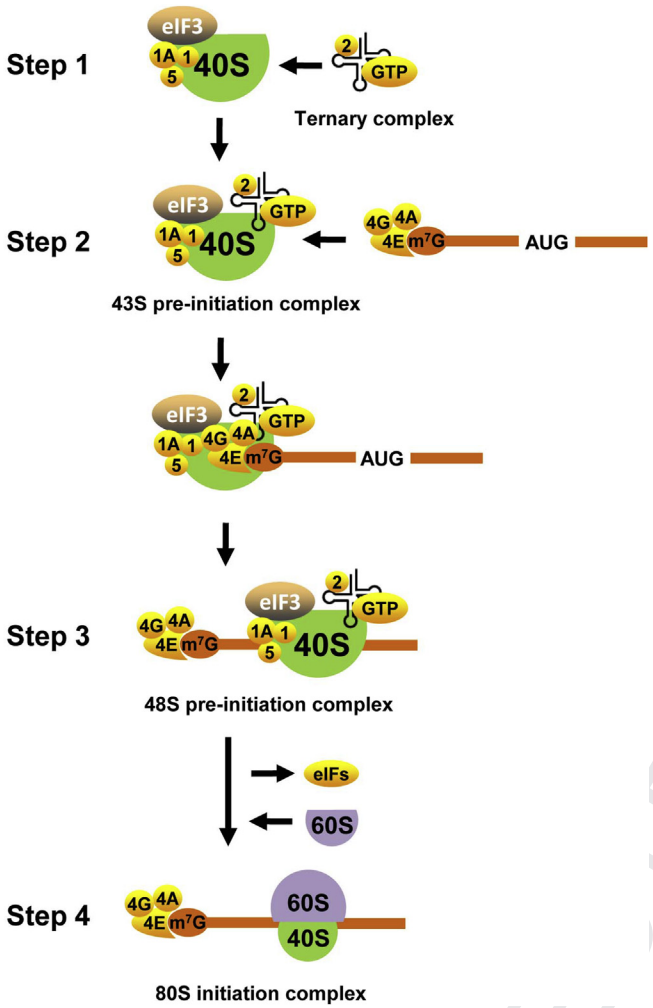

Fig. 3. Schematic model of four major steps of cap-dependent translation initiation in eukaryotes. Step 1: binding of the ternary complex to the 40S ribosomal subunit to form the 43S pre-initiation complex; step 2: introducing the complex of mRNA, eIF4B, and eIF4F to the 43S pre-initiation complex; step 3: scanning along mRNA to the start codon and forming the 48S pre-initiation complex; step 4: binding of the 60S ribosomal subunit to 48S pre-initiation complex and forming the 80S ribosome for elongation while releasing initiation factors. Initiation factors, ribosomes, 5′-cap structure (m^7G), the initiation codon (AUG), and mRNA are shown as self-explanatory symbols.

SHC, and Raf-1 [58]. Although it is unknown what causes this discrepancy in eIF3a regulation of DNA synthesis, EGF stimulation may overcome the eIF3a effect on basal DNA synthesis and it is also possible that eIF3a may regulate DNA synthesis through different pathways in different cell types used in these studies.

DNA repair is one of the key systems to maintain cell homeostasis and its activity is vital to cell survival following DNA damage. The major DNA repair systems include nucleotide excision repair, base excision repair, double-strand break repair, and mismatch repair. A number of chemotherapeutic drugs, such as cisplatin, kill tumor cells by creating DNA lesions. Cell survival against these drugs is largely attributed to the DNA repair capacity of the cells. Recently, it was found that eIF3a contributed to cellular sensitivity to cisplatin by suppressing nucleotide excision repair activity, the major mechanism to repair platinum-induced DNA damages [59,60]. It was determined that eIF3a suppresses the synthesis of key proteins in this pathway including xeroderma pigmentosum complementation group A (XPA), XPC, Rad23B, and replication protein A (RPA) and consequently, it sensitizes the cells to cisplatin [59,61].

Physiological and pathological process

Differentiation

The regulatory role of eIF3a in differentiation was first investigated in intestinal cells by using a mouse model [32]. eIF3a expression is mainly present in the fetus, but dramatically decreases or disappears in the postnatal stage. In the stomach and intestinal tissues, eIF3a expression negatively correlates with differentiation of epithelial cells. Further ectopic expression of eIF3a inhibits differentiation, whereas reduction of eIF3a expression promotes cell differentiation. This result indicates that eIF3a is a negative regulator of cell differentiation. The association of eIF3a with differentiation is also observed in tumors, with well-differentiated cancer cells showing substantially less eIF3a expression [62]. It is observed that eIF3a expression drops as the human colon cancer cell line CaCo-2 is induced to differentiate by confluency [32]. In tumor tissues, eIF3a expression is lower in the well-differentiated cancers from patients with cervical, bladder, and colon cancer [63–65]. Particularly in cervical cancer, eIF3a expression is completely lost after cells reach a differentiated status [64]. However, in gastric and esophagus cancers, eIF3a is highly expressed in well-differentiated tissues [66,67]. The reason for the different eIF3a expression patterns in different cancers is unknown; one possibility is that the correlation is variable in different cancers. Another study investigated the role of eIF3a in the benzo(*a*)pyrene inhibition of cell differentiation [68]. Benzo(*a*)pyrene impairs the differentiation of bone narrow-derived dendritic cells and down-regulates eIF3a, indicating the possible role of eIF3a as a positive regulator of differentiation. Obviously, these results together showed that the detailed role of eIF3a in differentiation is still not fully appreciated.

Fibrosis

Fibrosis is a pathologic change of disease-related injury with characterization of fibroblast proliferation and extracellular matrix accumulation [69]. It occurs in almost all major organs, including the lung, kidney, heart, liver, and skin. Recently, eIF3a was found to be involved in fibrosis through via regulation of the TGF-β1/SMAD3 signaling pathway [70–75]. TGF-β1 binds to the specific cell surface receptors to phosphorylate SMAD3 and subsequently regulates gene expression in the nucleus. The TGF-β1/SMAD3 signaling pathway plays a crucial role in the pathogenesis of fibrosis. In the rat model of pulmonary fibrosis, TGF-β1 induces expression of eIF3a and α-smooth muscle actin. In addition, eIF3a knockdown reverses the effect of TGF-β1 induced fibroblast proliferation and expression of α-smooth muscle actin, collagen I, and collagen III. In agreement with pulmonary fibrosis, eIF3a is also found to be up regulated in human renal fibrotic tissues and reduction of eIF3a inhibited TGF-β1 induced SMAD3 phosphorylation in the proximal tubular epithelial cell line HK-2 [76]. These studies together suggest that eIF3a may play a key role in the TGF-β1 induced fibrosis by mediating SMAD3 phosphorylation [73–75].

eIF3a and cancer

Over the past several years, eIF3a has been recognized as a proto-oncogene, which is the most important discovery in this field. It is suggested to be correlated with cancer occurrence, metastasis, prognosis, and therapeutic response. eIF3a is emerging as a new potential anticancer drug target in the eIF family (Fig. 4).

eIF3a and carcinogenesis

The accumulating evidence suggests that eIF3a is potentially a proto-oncogene and perhaps plays an important role in tumorigenesis. eIF3a is shown to be up regulated in the carcinomas of

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breast [62], cervix [64], esophagus [67], lung [22], stomach [66], colon [65], ovary [61], urinary bladder [63], oral cavity [77], and pancreas [78]. It has also been found that eIF3a polymorphisms may associate with cancer susceptibility of breast [9], stomach [12] and pancreas [79]. In addition, eIF3a expression is reported to be associated with metastasis of laryngeal and pancreatic cancers [78,80]. Ectopic overexpression of eIF3a promotes cell growth, malignant transformation, and apoptosis resistance [81]. Consistently, knocking down eIF3a impairs the ability of cell proliferation, colony formation, wound healing, migration and invasion in cancer cells of lung, urinary bladder and pancreas [57,63,78]. In the xenotransplanted mouse model of urinary bladder and pancreatic cancer, the tumor volume and weight of eIF3a-depleted xenografts is significantly decreased compared with that of tumors formed by control cells [63,78]. Based on these results, both *in vivo* and *in vitro* studies strongly suggest that eIF3a may be a proto-oncogene involved in tumorigenesis and metastasis.

As discussed previously, eIF3a may regulate synthesis of a subpopulation of proteins. Thus, it is possible that these proteins may mediate the proto-oncogenic function of eIF3a. Our previous studies identified some specific mRNAs under eIF3a regulation, including RRM2, α-tubulin, $p27^{kip}$, XPA, XPC, and RPA [56,57,59–61]. They are important molecules in the pathway of DNA synthesis and cell cycle and DNA repair, which are cellular processes related to tumorigenesis. We also identified that eIF3a bound the RPA2 5′ UTR to regulate its IRES activity, unveiling one of the mechanisms of eIF3a-regulating translation. A recent study used photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation sequencing technology to detect transcripts that interact with eIF3 at a genome-wide scale [82]. This study shows that eIF3a binds with 375 transcripts, most of which are involved in cell cycle, differentiation, apoptosis and growth, via 5′ UTR. All these studies suggest the presence of an eIF3a-targeting mRNA subset (ITRS) that is related to tumorigenesis cellular processes. eIF3a may induce oncogenesis by regulating the translation of ITRS members by binding with their 5′ UTR.

eIF3a and cancer prognosis

In addition to tumorigenesis, eIF3a is also widely reported to correlate with cancer prognosis. Patients with high eIF3a expression have better survival than those with low eIF3a in cancers of urinary bladder [63], cervix [64], ovary [61], esophagus [67], oral cavity [77] and lung [83]. However, the correlation of high eIF3a expression with better survival is not in agreement with what we expect of a proto-oncogene, and the mechanisms of eIF3a action in cancer prognosis largely remain unknown. Our previous study showed that eIF3a knockdown or overexpression, respectively, increased and decreased the cellular resistance to some anticancer drugs, including cisplatin, etoposide, and anthracyclines [77]. It is noteworthy that these drugs are major constituents of therapeutic regimens for cancers. Thus, we propose that eIF3a improves cancer prognosis possibly by regulating cellular response to some anticancer drugs.

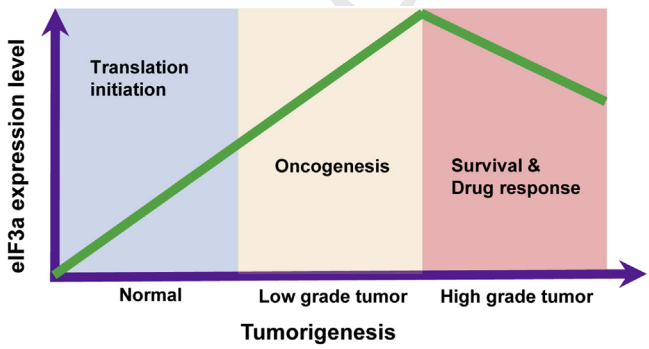

Fig. 4. Role of eIF3a in tumorigenesis. eIF3a expresses at a low level in normal tissues, increases significantly in the presence of cancer, and decreases again in high grade tumors. Some representative biological functions of eIF3a in normal, low-grade, and high-grade tumors are indicated accordingly.

eIF3a as a therapeutic target

A number of components in translational machine have been identified that correlate with carcinogenesis. Thus, targeting these molecules represents an attractive strategy for the treatment of cancer [84]. eIFs occupy the central stage of translational control and the detailed mechanisms of their action in malignant transformation is being revealed. Therefore, they are becoming a group of interesting and attractive targets for cancer therapeutic interventions [35]. Previous studies mainly focused on the eIF4F complex, which is composed of eIF4E, eIF4G and eIF4F. Inhibitors of eIF4A are identified by high-throughput screening, whereby phase II clinical trials of eIF4E antisense oligonucleotides in combination with chemotherapy are conducted [84,85]. As eIF3a is recognized as a proto-oncogene, it is also becoming a potential drug target for cancers. A couple of studies showed that knocking down eIF3a expression using antisense cDNA or small interfering RNA reversed the malignant phenotype of cancer cells [57,78]. The first compound identified as an eIF3a inhibitor is mimosine, which is a plant amino acid derived from *Mimosa pudica* seeds [56]. Mimosine treatment decreases eIF3a expression and further affects the translation of downstream genes. However, mimosine is a G1 phase blocker of cell cycle progression in mammalian cells and it is not clear if it selectively inhibits eIF3a expression. Thus, it may not develop into a drug targeting eIF3a. One group develops a series of compounds as eIF3a inhibitors based on pyridin-2(1*H*)-one scaffold [86]. Compared with mimosine, two compounds (NCE22 and NCE30) showed better eIF3a inhibition effect at the same or lower concentration. In addition, NCE22 showed good specificity in cancer cell growth inhibition, as indicated by the value of $IC_{50(NIH3T3)}/IC_{50(A549)}$. These compounds can be considered as candidate small molecule eIF3a regulators, which could be potential anti-cancer agents.

Conclusion and perspective

eIF3a is an important protein during translation initiation. It is observed to participate in a number of cellular, physiological, and pathological processes, including translation initiation, cell cycle, differentiation, fibrosis, carcinogenesis, and DNA synthesis and repair. However, the detailed role of eIF3a in these processes is unclear and constitutes one of the major directions for future study. An important discovery is that eIF3a is a potential oncogene, it is involved in cancer occurrence, metastasis, prognosis, and therapeutic response. However, to clarify the exact mechanisms of eIF3a oncogenic action remains a challenge. We proposed that eIF3a may induce oncogenesis by regulating the translation of a subset of cancer related mRNAs by binding with their 5′ UTR. As we gain deep insight into eIF3a physiological and pathological function, it is becoming a new potential drug target. Although some inhibitors are already developed and have good cancer cell growth inhibition, more efforts are still needed to improve current molecules or design new small molecule eIF3a regulators.

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Conflict of interest

None.

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