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Review

The eukaryotic initiation factor 3 and cancer

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ABSTRACT

Deregulated translation plays an important role in human cancer. Translation initiation factor eIF3 plays a central role in translation. Mammalian eIF3 is the largest of the initiation factors and exists as a protein complex with at least 13 non-identical subunits (eIF3a-m). The functions of the individual subunits have not yet been fully defined in mammals. It was suggested that mammalian eIF3 may consist of an active core of five subunits (eIF3a, b, c, g, i), with the remaining subunits serving to modulate eIF3 activity. Altering the expression level or the function of eIF3 may influence the synthesis of some proteins and consequently cause abnormal cell growth and malignant transformation. Seven eIF3 subunits have been implicated in human cancers. Our group has demonstrated reduced expression and loss of heterozygosity (LOH) of eIF3f in pancreatic cancer and melanoma. Recent studies also indicated that individual overexpression of 5 subunits of eIF3 promotes malignant transformation of NIH3T3 cells. eIF3a has been found to be overexpressed in breast, cervix, esophagus and lung cancer. eIF3b is significantly up-regulated in breast cancer. eIF3c is also found overexpressed in testicular seminomas. eIF3h was amplified and overexpressed in breast cancer and prostate cancer cell lines. Integration of MMTV into eIF3e/Int6 gene has been detected in breast cancers. Interestingly, reduced expression and LOH of eIF3e was recently found in human breast and lung cancers. Reduced eIF3e may increase eIF3 activity and protein synthesis. Therefore, deregulation of eIF3 subunits can contribute to tumorigenesis via induction of protein synthesis.

KEYWORDS: eIF3, translation, protein synthesis, cancer

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INTRODUCTION

Translation initiation factor eIF3 is the most complex factor which involved in the initiation of eukaryotic mRNA translation. Deregulated eIF3 plays an important role in human cancer. Altering the expression level or the function of eIF3 may influence the synthesis of some proteins and consequently cause abnormal cell growth and malignant transformation. Various subunits of eIF3 are known to regulate cell cycle progression and contribute to tumorigenesis. In this review, we focus on the recent progresses in the study of the role of eIF3 in oncogenesis of different human cancers.

1. eIF3

In eukaryotes, the process of translation is mainly regulated at the translation initiation level by initiation factors, the speed-limiting step of protein synthesis [1]. There are at least 12 translation initiation factor complexes (eIFs) involved in the initiation of eukaryotic mRNA translation [1, 2]. eIF3 is the most complex one which involved in ribosome biology and protein synthesis in eukaryotes. Various subunits of eIF3 are known

to regulate cell cycle progression and contribute to tumorigenesis [3]. In this review, we focus on the recent progresses in the study of the role of eIF3 in oncogensis of different human cancers.

1.1 Introduction of eIF3

eIF3 is first identified in the 1970s [4-6]. Pelham *et al.* [6] developed the nuclease-treated rabbit reticulocyte lysate system for assaying translation of exogenous mRNAs, and found that eIF3 translated all eukaryotic mRNAs accurately and efficiently from yeast, insect, plant and mammalian cells (although there were some viral RNA exceptions, notably poliovirus and rhinovirus RNAs). As investigations into initiation site selection mechanisms demand the study of a single RNA species, ideally coupled with the potential for mutagenesis, the use of cell free systems for such work was effectively limited to the study of wild-type viral RNAs. In 1984, Paul Krieg and Doug Melton [7] invented methods for transcribing cloned cDNAs using bacteriophage RNA polymerases, making it possible to study translation more efficiently.

1.2 The subunits of eIF3

eIF3 is a large protein complex with a molecular weight of about 550-700 kDa, consisting of 13 subunits known as eIF3a through eIF3m [1, 2, 8]. The 13 nonidentical subunits of eIF3 vary in function. Only five mammalian eIF3 subunits, eIF3a, eIF3b, eIF3c, eIF3g and eIF3i, are essential for translation *in vivo* [9-11]. The essential subunits constitute a conserved core complex that can carry out the crucial functions of eIF3. eIF3a is the largest subunit of human eIF3 and is thought to be the major subunit when purified initially from rabbit reticulocyte lysate [11]. eIF3e, localized in both cytoplasm and nucleus, is found to be identical to int-6 which is one of the frequent integration sites for mouse mammary tumor viruses (MMTV) [12]. Int-6/eIF3e was recently determined to be a part of the functional core of mammalian eIF3 [12-15]. The gene encoding eIF3h is located in the long arm of chromosome 8 (specifically, 8q23-24), a region that is frequently amplified in many tumor types [16]. eIF3j binds to the aminoacyl (A) site and mRNA entry channel of the 40S subunit, placing eIF3j directly in the ribosomal decoding center [17]. eIF3f is a member of the Mov34 family, which is involved in translation initiation, regulation of the proteasome and transcription [18].

1.3 The functions of eIF3

As we know, eIF3 plays a very important role in translation initiation and involves in all stages of initiation [1, 2]. It appears to have multiple roles, orchestrating the function of the other factors. Firstly, eIF3 can influence mRNA and tRNA binding by binding to 40S ribosomal subunit and inhibiting the association of 60S ribosomal subunit [19-22]. It is also involved in the scanning and selection of the initiation codon (AUG) process by disrupting interaction between eIF3 and eIF1/eIF5 [23, 24].

Secondly, eIF3 plays regulatory roles in initiating translation of a subpopulation of mRNAs. Different subunits of eIF3 may confer the core complex of eIF3 different functions and, consequently, effect on the initiation of translation of different mRNA species [25]. Recently, in late apoptotic cells, it was found that the partially degraded eIF3a relocates to membranes and acted as an apoptotic marker [26]. eIF3h is also predicted to be involved in regulating translation of some specific mRNAs [27]. The eIF3f subunit was recently found to be directly phosphorylated by $CDK11^{p46}$ *in vivo* [3, 28]. A Second eIF3f phosphorylation site (Thr119) by $CDK11^{p46}$ was identified during apoptosis [29]. It was shown that eIF3f plays an important role in regulating translation and apoptosis.

Thirdly, it has been observed that the expression level or activities of eIF3 associate with cell cycle regulation [30]. The global protein synthesis occurs mainly in the G1 phase of a cell cycle. eIF3a appears to play an important role in cellular responses to external cell cycle modulators likely by affecting synthesis of target proteins of these modulators. Dong *et al.* [31] examined the expression profile of eIF3a in cell cycle and its role in cell cycle progression. They found that eIF3a expression oscillated with cell cycle and peaked in S phase, indicating that eIF3a may be a translational regulator for proteins important for S phase entrance. Mutation of eIF3b inhibited global protein synthesis and also resulted in G1 phase arrest [32, 33]. The eIF3e subunit may be

involved in mitosis and segregation [34]. eIF3i overexpression stimulates the integration of growth signals by mTOR into the mRNA translation process, promoting protein synthesis and tumor growth [35]. eIF3k, located in both nucleus and cytoplasm, has been found to be a binding partner of cyclin D3. eIF3k may have additional function in regulating cell cycle by interacting with cyclin D3 [36].

2. eIF3 and cancers

More and more subunits of eIF3 have been found to have altered expression in human cancers. The progression of research about eIF3 demonstrated that altered expression of these eIF3 subunits play important roles in oncogenesis [37-39]. Although the mechanism by which altered expression of eIF3 contribute to human cancer development is not clear, it was thought that the unbalanced expression of eIF3 might cause changes in efficiency of translation of specific mRNAs that are normally translated at low efficiency and encode key proteins involved in cellular growth, angiogenesis, survival and malignancy [40]. eIF3 comprises at least 13 non-identical subunits of which only seven have been implicated in human cancers (eIF3a, b, c, e, f, h, and i) [41]. Increased mRNA and protein levels of the eIF3a,-3b, -3c, -3h, and -3i subunits have been detected in a wide variety of human tumors and are frequently identified as prognostic biomarkers for poor clinical outcome [42]. In contrast, eIF3e and eIF3f under-expression leads to stimulation of protein synthesis [3, 12, 43]. It was found that eIF3a mRNA increases in proliferative tissues such as bone marrow, thymus, and developing fetal tissues [44], eIF3b is over-expressed in human breast cancer [45], eIF3c is over-expressed in testicular seminomas [46]. High-level amplification of eIF3h has been found in prostate and breast cancers [16, 47, 48]. Also, over-expression of eIF3i has been reported to induce malignant transformation [49-51].

2.1 Breast cancer

Bachmann *et al.* [52] first identified that the expression level of eIF3a was increased in breast cancer tissues compared with paired normal mammary tissues. Dong *et al.* [44] found that altering the expression level of eIF3a changes the synthesis rate of both M2 and DNA. Decreasing eIF3a expression in human breast cancer cell line MCF7 significantly reversed their malignant growth phenotype. Olson *et al.* [53] evaluated associations between common inherited variation in these genes and breast cancer risk. Two hundred and five tagging and candidate functional single nucleotide polymorphisms in 30 genes required for normal cell division were genotyped in 798 breast cancer cases and 843 controls from the Mayo Clinic breast cancer study. They suggested that eIF3a play a direct role in the development of breast cancer. Cells transformed by over-expression of eIF3a show increased rates of proliferation and clonogenicity [44, 53]. Thus, it is hypothesized that the up-regulated expression of eIF3a changes the translational efficiency of a subset of mRNAs which encode proteins important for cell growth and oncogenesis [44]. Furthermore, the increased expression level of eIF3a was more observed with tumors at early invasive stages than later ones. Breast cancer patients with lower expression level of eIF3a had a better overall survival rate than the ones with higher eIF3a expression [44, 53].

The expression of eIF3i and eIF3b were also found to be increased in human breast tumors compared to their normal counterparts [45, 54]. However, decreased expression of Int6/eIF3e is observed in approximately one third of all human breast carcinomas [55]. The decreased expression of eIF3e in breast cancers could independently predict poor disease-free and overall survival [56]. The eIF3e gene was first identified as a common insertion site for mouse mammary tumor virus in virally induced mouse mammary tumors [43]. Mack’s group [56] found that targeted expression of a truncated form of Int6 to mammary epithelium in vivo results in a significant increase in mammary cancer risk. The mechanism of malignant transformation induced by the production of the truncated eIF3e is currently unknown. However, the fact that the wild type eIF3e is expressed in the cells expressing the truncated eIF3e suggests that the truncated eIF3e may act as a dominant negative oncoprotein [57]. eIF3e/INT6 and TID1 were shown significant positive correlation in all tissue types tested [43]. The presence of endogenous INT6 and TID1 proteins provides further evidence supporting a

cooperative role for INT6 and TID1 as complexes. These findings suggest cooperative roles for INT6, TID1, and patched proteins in cell proliferation, development, and tumorigenesis [43]. In fission yeast, the fact that Int6/eIF3e co-purifies with the eIF3 complex but is not essential for protein translation suggests that this subunit plays a regulatory role [56]. eIF3h is up-regulated in breast cancers. Using siRNA knockdown of eIF3h expression in a breast cancer (MDA436) cell line shows that lowering the level of eIF3h affects their malignant phenotypes [58]. These data support that high eIF3h levels help to establish and maintain the malignant state [54, 58].

2.2 Lung cancer

Lung cancer is the leading cause for cancer death in both male and female populations. Pincheira *et al.* [59] found that eIF3a is over-expressed in all types of human lung cancers compared to normal tissues. Some data show that the growth property of the antisense clones was remarkably different from that of vector-transfected control cells. Suppressing the overexpression of eIF3a can substantially change the malignant growth phenotype of H1299 lung cancer cell line [44]. Thus, eIF3a expression is important for lung cancer cell growth and overexpression of eIF3a is required for maintaining the malignant phenotype.

Buttitta *et al.* [60] investigated the prognostic role of Int6 in a large series of stage I non-small cell lung cancers (NSCLC) patients with long-term follow-up and found that Int6 RNA levels were reduced in 27% of the tumors. Low levels of Int6 RNA were found to be the only predictive factor of poor overall and disease-free survival. On the other hand, Asano *et al.* found that Int6 is identical to eIF3e [57]. Current evidence suggests that Int6 is a multifunctional protein that interacts with the eIF3, the proteasome and the COP9 signalosome to regulate activity or to mediate signals between them.

Recently, Cappuzzo *et al.* studied the amplification of eIF3h and MYC in NSCLC patients and found that over-expression of eIF3h was observed in 18.5% of the cases, and MYC was coamplified in all of these cases [40]. Both eIF3h and MYC positive patients have a higher response rate to chemotherapy and longer overall survival.

2.3 Pancreatic cancer

In human pancreatic cancer, it has been previously demonstrated that the heterozygosity of alleles is decreased on chromosome 11p15. Abraham, S. C. *et al.* [61] found 50% allelic loss at 11p15.4 in pancreatic acinar cell carcinoma by LOH. Fournet JC's group [62] found deletions in 11p15 in focal hyperplasia of islet cells of the pancreas in sporadic persistent hyperinsulinemic hypoglycemia of infancy but not in normal pancreatic cells. Deletions at 11p15.4 were also found by other groups in ductal pancreatic cancer as well as endocrine pancreatic cancer [63]. However, which specific gene is responsible for the tumorigenesis is not clear. Shi *et al.* [18] demonstrated for the first time that eIF3f is downregulated in pancreatic cancer. Then they found that overexpression of eIF3f inhibits tumor cell proliferation and apoptosis in pancreatic cancer cells. Shi *et al.* postulated that eIF3f is a negative regulator of translation and loss of eIF3f contributes to apoptosis resistance in tumor cells by deregulating translation [63].

Using a yeast two-hybrid screening strategy, they identified eIF3f as an interacting partner of the caspase processed C-terminal kinase domain of the cyclin-dependent kinase 11 ($CDK11^{p46}$) protein kinase [28] and demonstrated that eIF3f can interact with $CDK11^{p46}$ *in vitro* and *in vivo*. In order to investigate the molecular mechanism of the decreased expression of eIF3f in pancreatic cancer, Shi *et al.* [29] performed loss of heterozygosity (LOH) analysis in 32 pancreatic cancer specimens using three microsatellite markers encompassing the eIF3f gene. They showed that the prevalence of LOH ranged from 71% to 93%. They also performed eIF3f gene copy number analysis using quantitative real time PCR to further confirm the specific allelic loss of eIF3f gene in pancreatic cancer. Furthermore, RNA in situ hybridization and tissue microarray immunohistochemistry analysis demonstrated that eIF3f expression is significantly decreased in human pancreatic adenocarcinoma tissues compared to normal pancreatic tissues. These data provides new insight into the understanding of the molecular pathogenesis of the decreased eIF3f during pancreatic tumorigenesis. Recently, they demonstrated that eIF3f is directly phosphorylated

by CDK11^{p46} *in vivo* [29, 63]. These data suggested that eIF3f can inhibit cell proliferation and induces apoptosis in pancreatic cancer cells by increasing the binding to the eIF3 complex during apoptosis [29, 63, 64].

2.4 Prostate cancer

In developed countries, prostate cancer is the most commonly diagnosed nonskin malignancy in males. Multiple factors contribute to the high incidence and prevalence of prostate cancer. Risk factors include age, family history, and race. Studies using comparative genomic hybridization (CGH) have shown that about 70-90% of metastatic and/or hormone-refractory prostate cancers contain gain of 8q [65-68]. Nina *et al.* [69] identified the eIF3h gene, located at 8q23, as a candidate gene for the 8q amplification. They found that high-level amplification of eIF3h was in 30% of hormone-refractory prostate tumors and in 18% of primary tumors. The hormone refractory and locally recurrent tumors and metastatic prostate cancers expressed higher levels of eIF3h than primary tumors [40, 41]. The incidence of amplification was also higher in association with higher Gleason scores [41]. But siRNA treatment significantly inhibited the growth of the prostate cancer cell line PC-3 [70]. So, the increased expression of eIF3h associated with the stages. Recent studies have demonstrated that eIF3h and MYC are coamplified in prostate cancer, suggesting that there may be cooperation between MYC and eIF3h to further up-regulate translation initiation [40]. Overexpressed eIF3h may inhibit Myc-dependent induction of apoptosis of primary prostate cells. The study suggested that eIF3h may play an important regulatory role in translation of specific mRNAs.

In addition to the above mentioned cancer types, eIF3 also plays important roles in oncogenesis of other cancers. eIF3c expression is increased in testicular seminomas [71]. The eIF3f gene copy number is decrease in melanoma compared with normal tissues with a tumor/normal ratio of 0.52 [64].

3. Implication of eIF3

The subunits of eIF3 may play important roles in regulating translation of specific populations of mRNAs and cancer formation, also be important for regulating cell growth and cell cycle progression. But the mechanism of eIF3 subunits in oncogenesis and prognosis of cancer is not yet fully understood.

Shi *et al.* [29] demonstrated that enforced expression of eIF3f inhibits translation, cell growth, cell proliferation and induces apoptosis in pancreatic cancer cells. Some of these subunits of eIF3, such as eIF3a or eIF3f, may also be developed as therapeutic targets for better treatment of human cancers. Traicoff's data [43] suggested that the combination of INT6, TID1, and Patched protein levels may be useful biomarkers for the development of diagnostic assays. The addition of eIF3 to the list of initiation factors that may influence translation rates provides still another potential therapeutic target of intervention in the control of malignant growth. More vigorous studies on the role of eIFs in oncogenesis and cancer are needed, which will likely benefit diagnosis and prognosis of human cancers in the near future.

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