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Research progress of Eukaryon translation initiation factor 3 in Glioma

Lili Tang, Huanyu Zhao, Haicheng Xia*

The 3rd Affilated Teaching Hospital of Xinjiang Medical University (Affiliated Tumor Hospital), Urumqi, 830011, China
**Corresponding author: xiahaicheng@qq.com*

Abstract: *Glioma is the most common primary intracranial tumour and is characterised by high rates of disability, mortality and recurrence. Despite standard treatments such as surgery and adjuvant post-operative radiotherapy, the overall survival of gliomas remains low due to the presence of the blood-brain barrier and resistance to chemotherapeutic agents. Eukaryotic translation initiation factor 3 (EIF3) is involved in the genetic regulation of a variety of tumourigenesis, development and prognosis. In this review, we have reviewed the recent literature on the regulation of EIF3 expression in glioma and discussed the role of some EIF3 subunits in glioma.*

Keywords: *Eukaryon translation initiation factor 3, glioma*

1. Introduction

Glioma is the most common primary intracranial tumour. According to the US Brain Tumour Registry, gliomas account for approximately 80% of all central nervous system malignancies, with an annual incidence of approximately 5-8 per 100,000 and a 5-year mortality rate which is second only to pancreatic cancer and lung cancer among systemic tumours. At the same time, glioma is characterised by a high rate of disability, death and recurrence, which seriously affects the quality of life of patients and places a heavy economic and psychological burden on patients, their families and society as a whole. Gliomas can be classified into four grades, WHO I to IV, based on their growth rate, with grades I and II being low-grade gliomas, which are less malignant, such as astrocytomas, and grades III and IV being high-grade gliomas, which are extremely malignant, particularly glioblastomamultiform (GBM). Pseudonecrosis and microvascular proliferation are distinctive histological features that distinguish glioblastomas from lower grade gliomas and make them the most hypoxic and angiogenic of all tumours and the most aggressive. The current standard of care for gliomas, especially high-grade gliomas, is to excise the tumour as completely as possible while preserving the functional area, followed by radiotherapy and/or chemotherapy as appropriate, but the presence of the blood-brain barrier and the aggressive nature of the tumour's growth means that clinical outcomes for patients with gliomas remain generally poor. The median overall survival of patients with WHO grade IV glioblastoma-IDH-wild type is still only about 15 months, even after a combination of surgery, radiotherapy and chemotherapy. Although the prognosis for patients with low-grade gliomas is relatively good, over time most of these tumours can transform into treatment-resistant high-grade gliomas. Recently, there is increasing evidence that the expression of eukaryotic initiation factors 3 (EIF3s) is associated with malignancy, cancer prognosis and regulation of gene expression. Therefore, there is an urgent need to understand the molecular mechanism of EIF3s in the occurrence, development and prognosis of glioma, with a view to providing new ideas and theoretical basis for the diagnosis and treatment of glioma.

2. Structure and function of EIF3

In eukaryotic organisms, transcription of DNA, translation of RNA and protein synthesis are the main processes of gene expression, and abnormal regulation of any of these processes may lead to abnormal gene expression, which may eventually cause malignant changes in the organism. The translational initiation of RNA is the rate-limiting stage of protein synthesis and the key to the regulation of mRNA translation levels in eukaryotes, and the series of proteins involved in mRNA translation are known as EIFs. 12 EIFs have been identified, of which EIF3 is the largest (800 kDa) and most complex mammalian initiation factor. The mammalian eIF3 complex consists of 13 proteins. Of the 13 subunits of EIF3s, five

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(EIF3a, b, c, g and i) are conserved in all eukaryotes and are referred to as the conserved core, while the remaining eight subunits are considered non-core, with the eIF3-a, b, c complex fulfilling most of the functions of the eIF3s. The subunits of EIF3s are present in two specific structural domains, PCI (Prototeasome COP Signalosome Innitiation of translation) and MNP (Mpr1-Pad1 N-terminal). The PCI/MPN structural domain forms the core of the octameric structure of EIF3 (including EIF3a,c,e,f,g,h,l,k,m) and the remaining four subunits (EIF3b,d,g and i) are stably linked to the core of the PCI/MPN structural domain, which is present on the back of the 40S ribosome [1]. The subunits of EIF3 interface with the cap-binding EIF4 complex to form a 'bridge' that directs the 5' end of the mRNA towards the 40S ribosome. Mammals complete translation initiation through the interaction between these eukaryotic initiation factors (i.e. EIF3s), the 40S ribosomal subunit and the mRNA.

EIF3s play a central role in the eukaryotic translation initiation process and are the most important functionally and complexly structured protein factors. Translation initiation is a very complex process that requires the involvement of at least 10 translation initiation factor complexes [2]. EIF3s play an important role in protein translation in three main ways [3]. First, the eukaryotic translation initiation factor recruits the 40s ribosomal subunit to the 5' methyl guanosine cap, directs the 40s ribosome across the 5' untranslated region to the start codon and binds to the 60s ribosomal subunit to form the elongation-competent 80s complex [4], which then helps maintain the 40S ribosomal subunit in its free state while preventing the free 40S and 60S subunits from binding again. Secondly, EIF3s play a scaffolding role in the formation of the 43S pre-initiation complex, which promotes the formation of the GTP-EIF2-tRNA-methionine ternary complex mainly by binding to the 40S ribosome. Thirdly, EIF3s are involved in scanning and recognition of the initiation codon by stimulating mRNA binding to the 43S pre-initiation complex. EIF3s play an important regulatory role in the translation of mRNA core subgroups, in addition to participating in the process of mRNA translation initiation. It has recently been shown that altering the regulation of protein synthesis and translation may lead to selective translation of specific mRNAs, stimulating differentiation of tissue cells towards tumour cells, angiogenesis, tumour cell invasion and metastasis. Aberrant mRNA and protein expression levels of several EIF3 subunits were detected in several different solid tumours and tumour cell lines. For example, different isoforms of EIF3A were overexpressed in human breast, cervical, lung and gastric cancers, as well as in mouse melanoma and Hela cells; this EIF3A mRNA was overexpressed in tissues such as bone marrow, thymus and developing fetus; EIF3B and EIF3C were overexpressed in breast and testicular seminoma, respectively; and EIF3H was amplified at high levels in prostate tumours; In addition, EIF3I overexpression has been reported to induce malignant transformation of NIH3T3 cells. Insertion of the mouse mammary tumour virus (MMTV) genome into the EIF3E gene induces tumours in mice, suggesting a tumour-inducing role for EIF3E [5]. Xu et al[6] found that EIF3E was highly expressed in oesophageal cancer, and that high expression of EIF3E was closely related to the clinicopathological features of oesophageal cancer, patient prognosis, and the proliferation and invasive ability of tumour cells, and that the EIF3E gene could inhibit the proliferation and migration of tumour cells, suggesting that overexpression of EIF3E may be an important factor in determining tumour prognosis, and that targeting EIF3E therapy may become a direction with great potential.

3. Study of various subunits of EIF3s in glioma

Transcription and translation are the most fundamental and primary regulatory mechanisms in gene expression. Among them, the stages of mRNA translation are divided into three steps: initiation, elongation and termination. The regulation of translation control mainly occurs in the initiation phase, in which many subunits of EIF3s are involved in the process of mRNA translation and cell proliferation. Once any part of the expression regulation is abnormal, the protein expression in mammals may be abnormal, or even produce malignant tumours. More and more scholars are concerned about the important role of EIF3s in glioma, and the current studies related to some subunits of EIF3s in glial brain are summarized as follows.

1) EIF3A is one of the largest subunits of EIF3 and is located on chromosome 10q26, also known as p167, p180, p185, TIF32, elF3S10, elF3-p170, elF3-theta, etc. EIF3A is not required for translation, but it can play a regulatory role in protein synthesis of specific genes in order to reach the regulation of processes such as tumourigenesis, metastasis, cell cycle processes, drug response and DNA repair. Studies have shown that EIF3A plays an important role in regulating the synthesis and cell proliferation of proteins such as α-microtubulin, ribonucleotide reductase M2 and p27 [7]. The mRNA complexes of EIF4E, EIF4G, EIF4A and polyA binding proteins lack a secondary structure next to the m7G-cap and are taken to the 40S pre-initiation complex bound to Met-tRNAi, EIF1, EIF1A, EIF2, EIF3 and EIF5 through the interaction of EIF4G and EIF3. Further details have not been elucidated [8]. Several studies

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have found that EIF3A promotes tumourigenesis by negatively regulating the translation of p27/Kip1[9]. The p27 is a member of the cell cycle protein-dependent kinase inhibitors (CKIs) that regulate cell proliferation and cell cycle control [10]. EIF3A has been found to be expressed in many cancers, such as lung, breast [11], cervical [12], gastric and oesophageal cancers [13]. Kittler suggested that EIF3A knockdown leads to mitotic spindle defects [14], and that having two SNPs in this gene in a pure-hybrid variant (rs38248305 upstream and rs10787899 located in an intron) increases the risk of breast cancer by 50% compared to those without a copy of the SNP variant. EIF3A is also considered to be a key mediator of pancreatic cancer cell proliferation, migration and invasion. Specific shRNA knockdown of EIF3A significantly inhibits cell proliferation and clonogenic capacity in vitro and tumour growth in vivo [15]. However, Chai et al [16] found that EIF3A expression was reduced in high-grade gliomas by bioinformatic analysis and was associated with better overall survival, suggesting that EIF3A is an oncogenic factor in high-grade gliomas, but its mechanism of action in brain tumours is still lacking in-depth study.

2) EIF3B, also known as Prt1 homolog, P110, P116, eIF-3-Eta and eIF3-S9, is a highly conserved gene localised to chromosome region 7p22.3. The gene has 19 exons and 18 introns and encodes a 92 kDa protein consisting of 814 amino acids. The mammalian eIF3b protein contains two structural domains: the N-terminal domain (NTD), which consists of an atypical structured RNA recognition motif (RRM), and the WD40 β structural domain. The folded region of eIF3b-RRM in the human body is mostly negatively charged. RRM is a common structural motif that contains the conserved ribonucleoprotein1 (RNP1) and RNP2 sequences, which include conserved aromatic residues necessary for interaction with RNA. However, RNP2 of eIF3b in eukaryotes lacks aromatic residues and can only bind RNA in the presence of the entire eIF3 complex [1]. EIF3B is a major scaffolding protein that plays an important role in translational regulation, cell growth and tumourigenesis. EIF3B was found to be overexpressed in many malignancies, such as hepatocellular liver cancer (HCC), osteosarcoma, clear cell renal carcinoma (ccRCC) [17], bladder cancer, prostate cancer, esophageal squamous cell carcinoma (ESCC) [18], glioblastoma [19], colon cancer, cervical cancer [20], breast cancer and gastric cancer [21]. In ccRCC, ESCC, osteosarcoma, bladder cancer and glioblastoma, eIF3b inhibits cell proliferation by interfering with cell cycle progression and promoting apoptosis. It has been shown that knockdown of EIF3B levels by expression of lentiviral EIF3b-shRNA inhibited the proliferation of U87 cells, blocked G0/G1 phase progression and induced apoptosis, suggesting that EIF3B is an oncogenic key gene in glioma cells and could be used as a target gene for glioma therapy. It was also shown that knockdown of EIF3B gene may be associated with inhibition of DNA replication, suggesting that EIF3B may be a potential target for anti-glioma therapy [19].

3) EIF3C is also known as p110. In recent years, an increasing number of studies have demonstrated that eIF3c is an oncogene with tumourigenic properties and is able to be highly expressed in some tumour cells [22]. EIF3C is able to interact with the oncogene Merlin/NF2 and has a regulatory role in the pathogenesis of meningiomas. Zhao Qian et al [23] found by immunohistochemistry that EIF3C protein was expressed at moderate levels in normal tissues and at moderate and high levels in head and neck squamous cell carcinoma tissues, indicating that the high expression of EIF3C correlated with the clinicopathological grading of head and neck squamous cell carcinoma. Meanwhile, eIF3c is highly expressed in gliomas and has a similar positive correlation between expression and tumour pathological grade, playing a role in promoting tumour cell proliferation and invasion. In a retrospective study that included 83 glioma samples [24], the rate of EIF3c protein positivity in glioma tissue was found to be 83.13% (69/83), which was significantly higher than that in normal brain tissue. In addition, the positive expression rate of EIF3C protein in high-grade glioma (grade II and IV) and low-grade glioma was 91.07% and 66.67%, respectively, indicating that the positive expression rate of EIF3C protein correlated with the malignancy of glioma. The aberrant expression of eIF3c in glioma may affect the translation initiation process of glioma cells and participate in the process of glioma development, proliferation and progression, therefore, inhibition of EIF3C expression may become a new way to treat human glioma.

4) EIF3D, also known as p66, EIF3-p66 and EIF3-zeta, is one of the core subunits of EIF3s and plays an important role in maintaining the stability of EIF3. As a non-core subunit of EIF3, it has been little studied in depth in the past. Research in recent years has revealed that EIF3D may have the ability to inhibit HIV replication and there has been an increasing number of studies on the relationship between EIF3D and tumours. Knockdown of EIF3D was found to inhibit the proliferative capacity of prostate cancer, glioma, melanoma, colon cancer, kidney cancer, ovarian cancer and non-small cell lung cancer (NSCLC) [25-27], heralding the possible anti-tumour properties of EIF3D. Silencing EIF3D significantly induced clear cell renal cell carcinoma (CCRCC) cells to accumulate more cells in the sub-G1 phase, suggesting an increase in the percentage of apoptotic cells after knockdown of EIF3D [28]. Similarly, in U251 and U87 MG glioma cells, silencing EIF3D resulted in delayed cell growth and disrupted colony

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formation, induced cell cycle arrest in the G0/G1 phase, induced apoptosis through upregulation of Caspase-3 and PARP (both are apoptosis markers) expression, and reduced the migratory capacity of glioma tumour cells. Furthermore, EIF3D expression positively correlated with WHO classification of glioma, suggesting that EIF3D is involved in the progression of glioma [29].

5) EIF3E, also known as integration site 6 (INT6/p48), is localized to the human chromosome 8q22-q23 region and consists of 13 exons spanning the 45kb DNA genome, a component of the EIF3 complex that regulates translation initiation in mammals, located in the cytoplasm and nucleus, co-localizes with the PML proteasome, provides binding activity to the N terminus of proteins, and is involved in the positive regulation of mRNA binding activity, regulation of gene expression and initiation of translation. EIF3E is a P48 subunit that contributes to the stability of the entire EIF3 complex. EIF3E is functionally diverse and has been reported to be involved in biomolecular processes such as translation, mitosis, nonsense-mediated mRNA decay, and ubiquitin-mediated hydrolysis of fission yeast proteins. The oncogenic role of EIF3E in various malignancies remains controversial and may depend on the different stages and types of tumours. EIF3e silently inhibits the proliferation of human glioma cells by inducing cell cycle arrest and apoptosis. Bertorello et al [30-31] knocked down EIF3E in U251 (radiosensitive) and LN18 (radioresistant) GBM cell lines and found a significant increase in the proportion of apoptotic cells in both cell lines, indicating that silencing EIF3E led to increased sensitivity to radiotherapy in U251 and LN18 cells; they also found a decrease in the expression of hypoxia-inducible factors, mainly in the form of Hypoxia-inducible factors (HIF)-1α mRNA levels were reduced, indicating that EIF3E inhibited the translation of HIF-1α mRNA. HIFs are transcription factors consisting of two subunits, HIF-α and HIF-β, of which HIF-α consists of HIF-1α and HIF-2α (activation of HIF-2α is partially responsible for tumour formation). These factors control the transcription of over 150 GBM cell genes and are mainly involved in angiogenesis, metabolism, proliferation and cell migration. Reduced HIF expression and hypoxia reduce the cytotoxic effects of ionising radiation and limit the efficacy of radiation therapy. Bertorello's study confirmed that EIF3E promotes the malignant phenotype and progression of GBM by directly regulating the translation of specific mRNA subpopulations involved in the tumorigenic pathway. In addition to its potential prognostic value, EIF3E may also reduce the efficacy of glioma cells to radiotherapy by regulating the expression level of HIF, which may provide new ideas for standard radiotherapy/chemotherapy, and may improve the prognosis of GBM patients to some extent by developing specific new therapeutic agents to control changes in the EIF3E-regulated protein synthesis profile.

4. Conclusion

New advances have been made in molecularly targeted therapies for glioma, both basic and clinical, for example, ribavirin, an inhibitor of eIF4E, has been developed and bringing new hope for molecularly targeted therapies for glioma patients. In addition, the expression levels of eIF3d, eIF3e, eIF3f, eIF3h and eIF3l were highly correlated with the IDH mutation status of glioma, and the expression of eIF3b, eIF3i, eIF3k and eIF3m was positively correlated with WHO grade of glioma and negatively correlated with overall survival. The expression of eIF3i is an independent prognostic factor in IDH mutant low-grade gliomas and predicts the 1p/19q co-deletion status of IDH mutant LGG. High expression of eIF3i is closely associated with biological processes such as cell proliferation, mRNA processing, translation, T-cell receptor signaling, and NF-κB signaling [16]. EIF3s provide docking sites for protein kinases and participate in a variety of cellular pathways, such as the TGF-β and mTOR pathways. Several subunits such as EIF3D may regulate signalling molecules that mediate tumour cell migration and metastasis. The mechanism of the role of EIF3s in the development and progression of glioma remains poorly understood, and it is hoped that the role played by eIF3s in various stages of tumour development and related molecular mechanisms can be understood in greater depth in the future, and that novel anti-cancer drugs can be developed to address these discovered mechanisms.

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