CFIm25 in Solid Tumors: Current Research Progress

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Abstract
Cleavage factor I m25 is a newly discovered solid tumor-related gene, however, its precise role in cancer pathogenesis has not yet been characterized. Alternative polyadenylation is an RNA-processing mechanism that generates distinct 3'-termini on messenger RNAs, producing messenger RNA isoforms. Different factors influence the initiation and development of this process. As a key factor in alternative polyadenylation, cleavage factor I m25 plays an important role in messenger RNA maturation and cell signal transduction. Moreover, by regulating the process of alternative polyadenylation, it can inhibit the proliferation, invasion, and metastasis of a variety of tumors. Cleavage factor I m25 also acts as an oncogene in select tumors. The present review focuses on the role of cleavage factor I m25 in solid tumors and treatment. Due to the lack of current knowledge regarding the mechanisms of action and regulation of cleavage factor I m25 and alternative polyadenylation, it is necessary to further examine their role in cancer as well as in other diseases.

Keywords
cleavage factor I m25, tumor, gene, alternative polyadenylation

Abbreviations
ANXA2, annexin A2; APA, alternative polyadenylation; BC, bladder cancer; CCND1, cyclin D1; ceRNA, competitive endogenous RNA; CFIm25, cleavage factor I m25; circRNA, circular RNA; CPSF, cleavage and polyadenylation specificity factor; GBM, glioblastoma; HCC, hepatocellular carcinoma; IGF1R, insulin-like growth factor 1; LIMK2, LIM domain kinase 2; mRNA, messenger RNA; NF-κB, nuclear factor κB; NSCLC, non-small cell lung cancer; RHAMM, receptor for hyaluronan-mediated motility; RT-PCR, real-time polymerase chain reaction; UTR, untranslated region.

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Introduction
The 25 kDa subunit of the cleavage factor I m25 (CFIm25) is a key factor in alternative polyadenylation (APA) during pretranscriptional modification, whose inhibition can significantly promote the cutting of proximal poly(A) sites, allowing genes to escape negative regulation, thereby promoting cell proliferation and transformation.1 In the case of CFIm25, such evasion of negative regulation has primarily been detected in solid tumors, which is the focus of this review. Gene expression is subject to tight regulation via a complex process involving the genomic, transcriptomic, translational, and posttranslational levels. Among them, pre-messenger RNA (mRNA) processing is primarily accomplished by APA. This enables a single transcription unit to produce many different transcripts.2 Approximately 70% of human genes have the ability to undergo APA. By altering the site of action, multiple mRNAs with different sized 3'-untranslated regions (UTRs) can be produced, resulting in different functions, stabilities, localizations, and translational efficiencies.3 Further, compared with stable cells, genes are more likely to form

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shorter 3'-UTR mRNA in proliferating and transformed cells, resulting in the loss of many Cis-acting original sequences, such as negative regulatory targets rich in AU elements. This in turn results in improved mRNA stability and translational efficiency, promoting cell proliferation and transformation. Approxi-
mately 91% of genes expressed in tumor cells can form short 3'-UTR mRNAs, which likely contributes to their characteristic rapid proliferation and transformation. The process of APA requires the participation of many factors, including shear factor I (CFIm), shear factor II (CFIIm), cleavage and polyadenylation specificity factor (CPSF), and so on. Among them, shear factor I is composed of 3 peptides, 25, 59, and 68 kDa, designated CFIm25 (or CPSF5/NUDT21), CFIm59, and CFIm68, respectively. Cleavage factor I m25 plays an important role in preventing the cutting of polyA sites and promoting the formation of long 3'-UTRs. Hence, inhibition of the CFIm25 gene expression has been reported to be closely associated with certain diseases, including specific types of tumors. Specifically, it has been found that CFIm25 can inhibit tumor proliferation, invasion, and metastasis in lung cancer, liver cancer, bladder cancer (BC), testicular germ cell tumors (TGCTs), as well as other tumors. Inhibition of CFIm25 induced significant shortening of 3'-UTR in at least 1450 genes, of which 64% showed a significant increase in protein expression, promoting cell proliferation and transformation. Further, a dual function for CFIm25 has been described in human glioma and leukemia in that it functions as both a tumor suppressor and oncogene. The dual function of CFIm25 may be due to the use of tumor samples at different stages, which makes the true role of the gene uncertain. Hence, clarifying the role and mechanism of action employed by CFIm25 in various cancers may provide new avenues down which one might be able to explore the occurrence and development of tumors. The present review focuses on the role of CFIm25 in solid tumors and treatment.

**CFIm25 as a Tumor Suppressor in Many Solid Tumors**

**CFIm25 in lung cancer.** Lung cancer is one of the most dangerous malignant tumors to people’s health. Lung cancer is a malignancy with a high morbidity and mortality rate and affected patients have low survival and poor prognosis. In 2017, the most common incident cancers in men were nonmelanoma skin cancer (4.3 million incident cases) and tracheal, bronchus, and lung cancer. The genesis and development of lung cancers involve many signaling pathways with complex underlying molecular mechanisms involved in oncogene expression and promotion of abnormal cell proliferation. Hence, many aspects remain unknown. The activation of insulin-like growth factor 1 receptor (IGF1R) via cyclin D1 (CCND1) is critical in the development of lung cancer. Therefore, using the lung adenocarcinoma cell line, A549, Jingjing Huang et al inhibited the translation of CFIm25 via RNA interference and analyzed the subsequent changes in the IGF1R and CCND1. Their results showed that following inhibition of CFIm25, the proliferation of lung adenocarcinoma A549 cells increased. Furthermore, the 3'-UTR of IGF1R and CCND1 was shortened, and protein expression was increased. A 3'-UTR shortening of IGF1R was also observed in lung cancer samples compared to normal tissues, suggesting that this may be a mechanism by which protein expression is promoted in lung cancer. These results confirmed that the inhibition of CFIm25 promotes lung cancer proliferation and may be achieved by APA, resulting in shorter 3'-UTRs and increased IGF1R expression.

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers and is the leading cause of cancer-related deaths globally and is particularly prevalent in China. Zhujun Cheng et al found that a covalent CDK7 inhibitor (THZ1) dose-dependently inhibits proliferation, and significantly inhibits migration, of the human NSCLC cell lines, H1299, A549, H292, and H23. Furthermore, they reported that THZ1 treatment alters the expression pattern of glutaminase 1 subtypes by promoting the ubiquitination and degradation of CFIm25 thereby interfering with tumor metabolism and inhibiting NSCLC cell growth. Therefore, the combination of THZ1 and glutamine metabolic inhibitors provides a novel potential therapeutic strategy for the treatment of NSCLC. However, the molecular mechanisms employed by
CFIm25 to affect proliferation, invasion, and transformation of lung cancer cells remain to be further elucidated.

**CFIm25 in hepatocellular carcinoma.** Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third leading cause of cancer-related death. There is little information on the mechanisms involved in the pathogenesis of this disease. Diagnosis of HCC at early stages would be crucial for increasing the survival of patients. There are many factors involved in the development of HCC. Therefore, in-depth analysis of its associated molecular mechanisms may lead to novel intervention therapies.

Sheng Tan et al found that the expression of CFIm25 in HCC tissues was decreased compared with that of adjacent nontumor tissues; meanwhile patients with high CFIm25 expression had longer overall and disease-free survival compared to those with low expression. This suggests that CFIm25 has an inhibitory effect on human HCC. Yunwu Wang et al then went on to confirm that the expression of CFIm25 was related to tumor size, lymph node, and metastasis staging and progression of human HCC. First, they demonstrated that CFIm25 inhibits the proliferation of HCC cells via RNA interference. Secondly, transwell invasion and migration assays, as well as cell scratch assays, confirmed the inhibitory effect of CFIm25 on invasion and migration of HCC cells. In addition, through real-time polymerase chain reaction (RT-PCR), Western blotting, and luciferase reporter gene assays, they verified that CFIm25 inhibits HCC metastasis by inhibiting p38 and the JNK/c-JUN signaling pathway.

Additionally, Xiaojing Li et al reported that CFIm25 increases the formation of circular RNA (circRNA). Previous reports showed that circRNAs are related to HCC development. Many circRNAs have differential expression levels between tumor and nontumor tissues. It could be used as potential biomarker. However, this group demonstrated that CFIm25 knockdown effectively disrupted the competitive endogenous RNA (ceRNA) pathway (circRNA-microRNA-mRNA); meanwhile overexpression of the downregulated circRNA assisted CFIm25-mediated tumor suppression in HCC cells. Further, the loss of CFIm25 prevented cyclization of circRNA in HCC; in the absence of circRNA absorption, micro RNAs (miRNAs) were released to suppress tumor suppressor genes, leading to uncontrolled cell proliferation.

Taken together, these studies confirm the role of CFIm25 in inhibiting proliferation, invasion, and metastasis of HCC. It therefore represents a potential target for therapy and may also provide the basis for research into other digestive system tumors.

**CFIm25 in osteosarcoma.** Osteosarcoma is the most common bone tumors which consisted of malignant mesenchymal cells generating osteoid and immature bone. It has been shown that osteosarcoma is common in children and adolescents and shows high mortality rate. Although the causes of osteosarcoma have not yet been fully elucidated, there is probably a correlation between the rate of bone growth during puberty and the incidence of this disease. Despite several attempts to improve therapeutic response, the rate of survival for osteosarcoma has not changed during the past 3 decades. Therefore, the discovery and developing new effective therapeutic platforms are required. Elucidating the molecular mechanism of this disease will not only provide improved understanding of its pathogenesis and progression but will also help identify new targets for effective therapies. MicroRNAs arc a group of small endogenous noncoding RNAs involved in many cancers and various cellular processes such as cellular growth, DNA methylation, apoptosis, and differentiation. There are many evidences that the various miRNA expressions in osteosarcoma cells are dysregulated, so it can propel a normal cell to cancerous one by influencing the cell survival, apoptosis, and autophagy, and eventually increased chemoresistance. Hence, miRNAs can be considered as new biomarkers for osteosarcoma diagnosis, and according to the role of autophagy in osteosarcoma progression, miRNAs can use inhibiting or promoting autophagy agents.

To this end, Zhongjiao Zhu et al found that mir-181a (a short noncoding RNA) was expressed at higher levels in osteosarcoma tissues compared to adjacent normal tissues, while CFIm25 expression was reduced in adjacent normal tissues. Furthermore, they confirmed that mir-181a could inhibit the expression of CFIm25 in osteosarcoma cells, while promoting the proliferation of and inhibiting apoptosis in osteosarcoma cells.

**CFIm25 in BC.** Bladder cancer is the ninth most common malignant tumor in the world and is a leading cause of cancer-related deaths, with 400 000 new cases diagnosed every year and 165 000 deaths per year. Ming Xiong et al reported decreased expression of CFIm25 in BC tissues and cells; meanwhile the total survival and recurrence free survival of patients with BC were longer with higher CFIm25 expression compared to those with low expression. The overexpression of CFIm25 significantly inhibits the proliferation, migration, and invasion of BC cells, while knockout promotes their proliferation, migration, and invasion. By regulating the expression of CFIm25, several genes with shortened 3'-UTRs were identified, and further, it was found that CFIm25 regulated the expression of Annexin A2 (ANXA2) and Lim Domain Kinase 2 (LIMK2) in the Wnt/β-catenin and nuclear factor κB (NF-κB) signaling pathways. These findings suggest that CFIm25 plays a key role in BC progression, at least in part through ANXA2 and LIMK2, the latter through APA. Therefore, CFIm25 may prove effective as a diagnostic and therapeutic target for BC.

**CFIm25 in germ cell tumors of the testis.** Testicular germ cell tumors are the most common cancer type in young men. These tumors can be divided into 2 main histological subtypes: seminoma and nonseminoma, with seminoma as the more common type. Although the etiology of TGCT is poorly understood, it has been reported that in the testis, planar division of undifferentiated germ cells is an important event, which is regulated by the receptor for hyaluronan-mediated motility (RHAMM).
When this process is disrupted, testicular atrophy and low fertility can result as well as the development of TGCTs occurs. Receptor for hyaluronan-mediated motility has 2 mitotic functions, the first is in defining the orientation of the spindle, and the second is in the retention of its integrity.\(^3^2\) Huaibiao Li \textit{et al} confirmed that downregulation of RHAMM mRNA and spindle protein dissociation occur at an extremely high rate (96\% in the latter) and were significantly altered \(P < .001\) in human seminoma. Moreover, CFIm25 has been shown to positively regulate the stability of its RHAMM mRNA. Hence, if the expression of CFIm25 becomes inhibited, the translation of RHAMM decreases, leading to testicular atrophy and a low fertility rate, both of which are related to the occurrence and promotion of TGCTs.

**Different Functions of CFIm25 in Leukemia and Glioblastoma**

Although the inhibitory effect of the CFIm25 gene on a variety of tumors has been confirmed, it has the opposite effect in specific tumors. This phenomenon may be the cause of experimental differences, including collection of specific tumor samples from different sources or at different disease stages. Nonetheless, it is important to note that this gene has been reported to have a role both as a tumor suppressor gene and an oncogene. CFIm25 in leukemia. Leukemia or cancer of blood is a well-known cancer, which affects a range of people from newborns to the very old. It is a public health problem throughout the world. By way of treatment, due to the lack of specific anticancer therapies, common treatments of leukemia lead to severe side effects. Non specific anticancer drugs result in inhibition of normal cell growth and thereby their necrosis. Thus, finding new treatments for leukemia is essential.\(^3^4\) For instance, Zhang \textit{et al} reported that the mRNA expression levels of CFIm25 are higher in patients with primary chronic myelocytic leukemia and K562 leukemic cells compared with healthy controls and peripheral blood mononuclear cells. In fact, downregulation of CFIm25 in leukemia is essential. \(^3^4\) For instance, Zhang \textit{et al}\(^3^5\) reported that the mRNA expression levels of CFIm25 which are higher in patients with primary chronic myelocytic leukemia and K562 leukemic cells compared with healthy controls and peripheral blood mononuclear cells. In fact, downregulation of CFIm25 expression in K562 cells inhibits their proliferation and promotes apoptosis. Subsequent studies confirmed the role of CFIm25 in promoting K562 proliferation through the regulation of p-ERK expression. These findings may provide insights into the molecular mechanisms underlying the effects of CFIm25 on leukemia cells and help researchers to elucidate novel strategies for the treatment of leukemia.

**CFIm25 in glioblastoma.** Glioblastoma (GBM) is the most common type of primary central nervous system tumor in adults. Its treatment is primarily based on surgical, radiotherapy, and chemotherapy interventions, however, prognosis is often poor, with a 5-year survival rate of only 9.8\%.\(^3^6\) Despite serious efforts worldwide, it remains a deadly disease which is associated with poor prognosis. Multiple lines evidence indicated that deregulation of a variety of cellular and molecular pathways is related to it.\(^3^7\) The mechanism of GBM has been widely studied and is generally believed to be closely associated with low expression of tumor suppressor genes or high expression of oncogenes. Specifically, in GBM, the downregulation of CFIm25 leads to enhanced tumorigenesis and increased tumor size. Alternatively, the overexpression of CFIm25 leads to a reduction in these properties and stunts tumor growth.\(^3^8\) Additionally, Masamha \textit{et al}\(^3^9\) evaluated the length of 3 genes (CCND1, DICER1, and TIMP2) by RT-PCR and subjected them to polyadenylation. They found that during polyadenylation, depletion of CFIm25 led to a shortening of the 3'-UTRs of all 3 genes. To further confirm the role of CFIm25, Masamha \textit{et al} collected GBM samples from the cancer genome map (TCGA) and stratified them based on GFIm25 expression level. They observed a positive correlation between the expression of CFIm25 and the length of the 3'-UTR in GBM, that is, when CFIm25 expression was low, the 3'-UTR was short. Moreover, in GBM cell lines with low CFIm25 expression, the expression of CFIm25 was artificially increased, resulting in a corresponding increase in 3'-UTR length, while inhibiting cell proliferation and tumor growth in mice. Alternatively, in GBM cell lines with high CFIm25 expression, reduced CFIm25 expression resulted in a shortened 3'-UTR, while promoting cell proliferation and tumor growth in mice. The above experiments indicate that CFIm25 is a tumor suppressor promoting growth by elongating the 3'-UTR in GBM, which may serve as a potential target gene for tumor therapy. In addition, studies from Jia-Cheng Lou \textit{et al}\(^4^0\) and others have shown that the NF-κB pathway is associated with GBM development. Using a combination of gene set enrichment analysis, Western blotting, and RT-PCR analysis, they showed that CFIm25 has a significant role in the organization of human brain gliomas, and that it likely functions through an NF-κB dependent pathway resulting in glioma cell proliferation. This suggests that CFIm25 is an upstream regulatory factor in the NF-κB pathway and may represent a useful potential molecular marker for the GBM mesenchymal subtype. These findings provide strong evidence that CFIm25 may serve as a novel target for the treatment of glioma.

**Summary and Future Prospective**

With the development of society and technology, the concept of diagnosis and treatment of cancer is changing fundamentally. The early diagnosis and treatment of cancer depends on new discoveries about the role of genes and molecular pathways. A growing body of evidence has shown that APA contributes to the regulation of gene expression in different physiological states. Alternative polyadenylation, together with alternative splicing, increases the complexity of gene expression regulation. Untangling this complexity may provide novel insights for cancer research and the identification of potential new therapeutic targets. As a critical molecule in this process, CFIm25 plays an essential role in tumor cell regulation, and thus, related research is becoming more common.

At present, although the mechanism of CFIm25 in nontumor and tumor cells is not fully understood, it has been shown to
exert both an oncogene and tumor suppressor gene function in tumor tissues from different sources and disease stages. It may, therefore, also contribute to the development of tumors. Hence, an in-depth study on the relationship between APA and the regulation of multiple CFIm25 targets will better inform the process of gene expression regulation and is expected to increase our understanding of tumors, leading to new directions for early diagnosis and effective novel treatments.

**Authors’ Note**

Our study did not require an ethical board approval because it did not contain human or animal trials.

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