Neoplasma 2024; 71(5): 442–450

doi:10.4149/neo_2024_240603N242

Exploring the role of eIF3m in prostate cancer: regulation of c-Myc signaling pathway and therapeutic implications

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Received June 3, 2024 / Accepted October 21, 2024

Prostate cancer (PCa) is the most frequently diagnosed malignant tumor in males, and there are currently few effective therapeutic targets following hormone therapy resistance. Subunits of eukaryotic initiation factor 3 (eIF3) have been implicated in the progression of various cancers. This study aims to investigate the biological functions of the eIF3m subunit in PCa and assess its potential as a novel therapeutic target for treatment. We utilized open-access datasets and patient tissues to analyze the expression and prognostic value of eIF3m in PCa. To explore the role of eIF3m in PCa growth, we established eIF3m knockdown models in PC3 and 22Rv1 cells for both in vitro and in vivo studies. Gene set enrichment analysis (GSEA) was utilized to identify signaling pathways regulated by eIF3m in PCa. Additionally, western blotting and immunochemistry were used to confirm the regulation of c-Myc signaling by eIF3m in PCa. Our results indicated that eIF3m expression was elevated in PCa tissues, with higher levels correlating with an increased risk of biochemical recurrence following radical prostatectomy. Both in vitro and in vivo experiments demonstrated that inhibiting eIF3m significantly impeded the growth of PCa cells. GSEA and immunochemistry further revealed that high eIF3m expression contributed to the activation of c-Myc signaling in PCa patients. Notably, the downregulation of eIF3m resulted in a significant decrease in the expression of c-Myc mRNA and protein in PCa cells. Overall, our findings suggest that eIF3m inhibition significantly suppressed PCa cell growth and c-Myc signaling, indicating that eIF3m is a promising therapeutic target for PCa patients.

Key words: c-Myc; prostate cancer; eIF3; eIF3m; proliferation

Prostate cancer (PCa) remains the most frequently diagnosed malignant tumor and the dominating cause of cancer-related death among males worldwide [1, 2]. As the growth of PCa is initially hormone-dependent, androgen deprivation therapy (ADT) is effective at the initial stage. However, PCa patients receiving ADT treatment inevitably relapse into castration-resistant prostate cancer (CRPC) within a few years [3, 4]. Regrettably, it is reported that patients with CRPC have a median survival of no more than 20 months [5, 6]. Next-generation antiandrogens (e.g., abiraterone and enzalutamide) [7, 8] and chemotherapies (e.g., docetaxel) [9, 10] are efficacious for CRPC patients, but inherent or acquired resistance to these treatments and even development of neuroendocrine prostate cancer remains a therapeutic challenge [11, 12]. Poly (adenosine diphosphate-ribose) polymerase inhibitors, like olaparib, may work in these patients, but mostly in patients with alterations in genes involved in homologous recombination repair [13]. Therefore, it is imperative to develop novel therapeutics for PCa.

Recent studies have made significant advancements in understanding the genes and mechanisms associated with PCa progression. For example, it has been reported that the CCDC7 circular RNA, which encodes a protein, inhibits the progression of PCs by upregulating FLRT3 [14]. Lysine methyltransferase SMYD2 is associated with poor prognosis in PCa, promoting cell growth and resistance to enzalutamide treatment, making it a potential therapeutic target [15, 16]. Additionally, autocrine IL-11 mediates resistance to docetaxel in PCa through the activation of the JAK1/STAT4 pathway [17]. MT1G, a ferroptosis-related gene that can influence the immune microenvironment of PCa, is decreased in PCa tissues, and its expression levels correlate

with responses to immune checkpoint inhibitor therapy [18]. Furthermore, the cell cycle kinase CDC7 was identified as a critical gene related to neuroendocrine transformation in PCa. Inhibition of CDC7 suppresses neuroendocrine transdifferentiation and extends responses to targeted therapy by inducing proteasome-mediated degradation of the MYC proto-oncogene (MYC), which is implicated in stemness and histological transformation [19].

Eukaryotic initiation factor 3 (eIF3) is the largest (800 kDa) and the most complex translation initiation factor in human cells; it consists of 13 unique subunits (a–m). eIF3 has a pivotal role in the initiation of protein translation that bridges the 43S pre-initiation complex [20]. Recent studies have demonstrated that eIF3 subunits are essential for the development of various tumors, including PCa [21]. For example, eIF3a regulates the PI3K/AKT signaling to promote the progression of colorectal cancer [22]. eIF3b is identified as a novel oncogenic factor in PCa, involved in the proliferation of PCa cells [23], FOXA1/PUS1 mediated PCa bone metastasis [24], and castration resistance and immune evasion of PCa [25]. eIF3c promotes PCa cell metastasis through the MAPK pathway [26]. eIF3d promotes stem cell-like properties of cervix cancer cells by promoting FAK activation through GRP78 [27]. eIF3f knockdown inhibits PCa cell growth by suppressing the Akt signaling [28]. Notably, as the last defined subunit, eIF3m plays a crucial role in maintaining the integrity of the eIF3 complex [29] as well as affecting ribosome biogenesis and transcription [30]. However, the involvement of eIF3m in PCa remains unknown.

In the present study, we demonstrated that eIF3m is upregulated in PCa tissues and high expression of eIF3m predicts a higher risk of biochemical recurrence after radical prostatectomy. Knockdown of eIF3m inhibits PCa cell growth both *in vitro* and *in vivo*. Furthermore, eIF3m is positively correlated with c-Myc signaling in PCa and eIF3m disruption downregulated the mRNA and protein expression of c-Myc. Overall, these results suggest that eIF3m could contribute to PCa progression by regulating c-Myc signaling.

Materials and methods

Cell culture. The PC3 PCa cell line was acquired from the American Type Culture Collection (Manassas, VA, USA). The 22Rv1 PCa cell line was obtained from the Stem Cell Bank, Chinese Academy of Sciences (Shanghai, China). Both PC3 and 22Rv1 cells were cultured in RPMI-1640 medium (C11875500BT; Gibco) supplemented with 10% fetal bovine serum (16000044; Gibco) and 1% penicillin/streptomycin (15140-122; Gibco). These cells were cultured at 37 °C in a humidified incubator with 5% CO_2.

Plasmids and lentiviral infection. The short hairpin RNA (shRNA) sequences targeting human eIF3m, namely sheIF3m#1 (5'-CAGGTGTATTGTACGAGCATT-3') and sheIF3m#2 (5'-CTTCAGATTGGAGCTGATGAT-3'), along with a scrambled shRNA sequence (shCON, 5'-GCTCCGTGAACGGCCACGAGT-3'), were cloned into the pLKO.1 vector (Addgene; 10879). The psPAX2 plasmid (Addgene; 12260) and pMD2.G plasmid (Addgene; 12259), in conjunction with the pLKO.1 plasmids harboring these specific sequences, were transfected into HEK293T cells using polyethylenimine (Polysciences; 23966-1) according to the manufacturer's instructions, to generate lentivirus. PC3 and 22Rv1 cells infected with the lentivirus were subsequently treated with puromycin (5 μg/ml) (Sigma-Aldrich, St. Louis, MO, USA) to select for stably transformed cell lines.

Western blot analysis. Cellular proteins were collected by solubilizing the cells in lysis buffer after washing the cultured cells twice with phosphate-buffered saline. Approximately 40 μg of protein for each sample was separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred onto polyvinylidene fluoride membranes. The membranes were blocked with 5% bovine serum albumin in Tris-buffered saline with 0.1% Tween 20 (TBST) before incubation with primary antibodies overnight at 4 °C. The primary antibodies used included eIF3m (11423-1-AP; Proteintech; 1:1000), β-actin (sc-47778; Santa Cruz Biotechnology; 1:1000). c-Myc (10828-1-AP; Proteintech; 1:1000). After three washes with TBST, 10 min each, the membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies at room temperature for 1 h. Following three additional washes in TBST (10 min each), the signal was visualized using a chemiluminescence reagent (P0018FS, Beyotime, China).

Cell growth and colony formation assay. The PC3 cells and 22Rv1 cells, each at a density of 1,500 cells/well, were seeded in 96-well plates and evaluated at the designated time points. The evaluation was performed by incubating the cells with 10% Cell Counting Kit-8 (CK04; Dojindo) reagents for 3–4 h and then measuring the optical density (OD) at 450 nm. Additionally, both PC3 and 22Rv1 cells, at 1,000 cells/well, were plated in 6-well plates and cultured for 8–12 days until colonies reached an appropriate size. The colonies were then fixed with methanol for 10 min and stained with 0.1% crystal violet for 20 min.

Patient tissues and immunohistochemistry (IHC). Thirty PCa tissues and twenty adjacent normal prostate tissues were collected from patients at Shuguang Hospital Affiliated with the Shanghai University of Traditional Chinese Medicine. The collection was done with full disclosure and informed consent from the donors. The research protocol was approved by the Medical Ethics Committee of Shuguang Hospital Affiliated with the Shanghai University of Traditional Chinese Medicine following the Declaration of Helsinki (Approval No. 2022-1184-121-01). IHC was performed using an IHC kit (abs957; Absin) according to the manufacturer's protocol. Antibodies targeting eIF3m (11423-1-AP; Proteintech; 1:100) and c-Myc (10828-1-AP; Proteintech; 1:100) were used. Each sample was evaluated based on the staining intensity (0: negative, 1: weak, 2: moderate,

and 3: strong) and the proportion of positive cells (0: 0%, 1: 1–25%, 2: 26–50%, 3: 51–75%, and 4: 76–100%). The final IHC score was calculated by multiplying the intensity score by the percentage score. For samples with heterogeneous staining intensities, the scores for each staining level were multiplied by the corresponding percentage score and then summed to obtain the final score.

Animal experiments. To establish the tumor-bearing mouse model, 5×10^5 PC3 cells, either with stable knockdown of eIF3m or intact, were suspended in Matrigel (volume, 1:1; 356234; Corning, Inc.) and subcutaneously implanted into 6-week-old male athymic nude mice (n=5/group). Tumor sizes were externally measured using a caliper every four days, and tumor volumes were calculated using the formula: Length × width × width /2. After 32 days, the mice were euthanized, and the xenografts were excised and weighed. The animal care and experiment protocols were approved by the Animal Ethical Committee of the Shanghai University of Traditional Chinese Medicine (Approval No. PZSHUCTM220724203).

Published datasets and analysis. TCGA expression profiles were obtained from UCSC Xena (http://xena.ucsc.edu/). mRNA expression datasets GSE62872, GSE70770, and GSE6919 were downloaded from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). When published datasets were assessed by GSEA software (Version 4.1.0), the Pearson metric was used to rank genes and the phenotype permutation type was used; for all other parameters, default settings were used. Hallmark gene sets from the Molecular Signatures Database (version 2022.1) were used in the analyses.

Statistical analysis. Statistical analyses were conducted using GraphPad Prism software (version 8) and R software (version 4.1.0). Quantitative data from experiments involving biological replicates are expressed as mean ± SD or mean ± SEM. The employed statistical methods include ANOVA, Student's t-test, and Spearman's correlation analysis to evaluate the relationships between variables, as well as Kaplan-Meier and Cox regression analyses for survival data. Statistical significance was established at a p-value <0.05. Significance levels are indicated as $^*p<0.05$, $^{**}p<0.01$, and $^{***}p<0.001$.

Results

eIF3m is associated with the development of human PCa. To explore the eIF3m expression level in PCa, the eIF3m expression in normal prostate tissues and prostate tumor tissues from the TCGA PRAD dataset was analyzed. We found that eIF3m expression was significantly higher in PCa tissues compared to non-tumor prostate tissues (Figure 1A). This finding was corroborated by the analysis of three additional PCa datasets from the GEO database (Figures 1B–1D). Moreover, a higher expression of eIF3m was observed in metastasis prostate cancer tissues than in primary prostate cancer tissues (Figure 1D). We also assessed eIF3m protein levels in patient tissues via IHC and confirmed elevated eIF3m expression in PCa tissues compared to non-tumor prostate tissues (Figures 1E, 1F). Lastly, we explored the prognostic value of eIF3m using the open-access PCa dataset GSE70770. Kaplan-Meier analysis revealed that the higher eIF3m levels were associated with an increased likelihood of biochemical recurrence following radical prostatectomy (Figure 1G). After adjusting for PSA, Gleason score, positive surgical margin, extracapsular extension, and pathological T stage, high eIF3m expression remained an independent risk factor for biochemical recurrence (Figure 1H).

eIF3m knockdown inhibits PCa cell growth *in vitro*. To explore the role of eIF3m in PCa cell proliferation *in vitro*, we established eIF3m stably silenced PC3 and 22Rv1 cells. Western blot analysis demonstrated that the two shRNAs targeting eIF3m effectively reduced eIF3m protein expression compared to the control group (Figure 2A). Cell proliferation was assessed using the CCK-8 assay, and the results showed that silencing eIF3m significantly decreased the growth of both PC3 and 22Rv1 cells (Figure 2B). Consistently, in the cell viability experiments, eIF3m knockdown markedly reduced the number of cell colonies in both PC3 and 22Rv1 cells (Figures 2C, 2D). Taken together, these results support the hypothesis that eIF3m plays a crucial role in the growth of PCa cells.

eIF3m depletion suppresses PCa cell growth *in vivo*. In order to demonstrate the effects of eIF3m on PCa growth *in vivo*, we established a xenograft model by subcutaneous injecting PCa cells with or without stable eIF3m knockdown into the flank of 6-week-old male nude mice. Consistent with the *in vitro* findings, eIF3m silencing significantly reduced the growth of PC3 xenografts (Figure 3A). After a 32-day follow-up, all mice were euthanized and the xenografts were harvested. The xenografts from the eIF3m knockdown group were notably smaller (Figure 3B) and weighed less than those in the control group (Figure 3C). These results confirmed that eIF3m is essential for PCa cell growth *in vivo*.

eIF3m affects the activation of c-Myc signaling in PCa. To investigate the potential underlying mechanism by which eIF3m regulates PCa cell growth, we conducted hallmark pathway enrichment analysis using the GSEA method on published PCa datasets. The results, including enrichment scores, normalized enrichment scores, and p-values, are presented in rank order. Notably, the c-Myc-upregulated gene set emerged as the most significantly enriched in patients with high eIF3m expression, as evidenced by the analyses of the GSE62872 and GSE6919 datasets (Figures 4A, 4B). Additionally, other PCa datasets, including TCGA and GSE70770, were utilized for GSEA, further confirming the enrichment of c-Myc signaling in PCa tissues with high eIF3m expression (Figure 4C). Taken together, these results suggest that eIF3m enhances the activity of oncogenic c-Myc signaling in PCa, thereby promoting tumor progression.

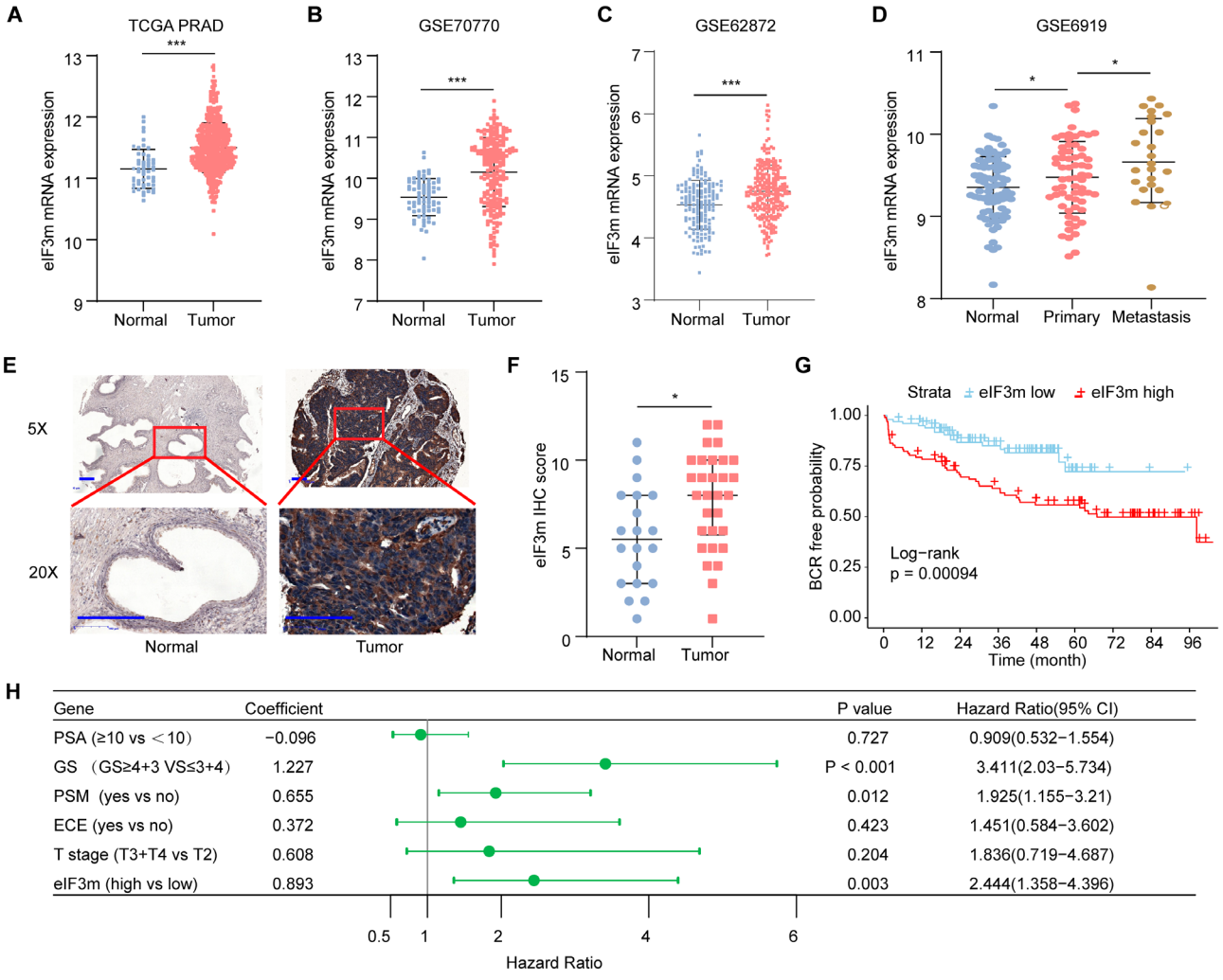

Figure 1. eIF3m is associated with the development of human PCa. A–D) The transcriptional level of eIF3m in four independent studies revealed from (A) TCGA prostate cancer (PRAD) (normal, n=52; tumor, n=498), (B) GSE70770 (normal, n=74; tumor, n=219), (C) GSE62872 (normal, n=160; tumor, n=264), and (D) GSE6919 (normal, n=81; primary tumor, n=65; metastasis tumor, n=25). Mean ± SD, Student's t-test. E) Representative photographs of normal prostate tissues and PCa tissues stained with eIF3m antibody by IHC. Scale bar: 100 μm. F) eIF3m IHC scores in normal prostate tissues and PCa tissues (normal, n=20; tumor, n=30; Mann-Whitney test). G) Survival plots showing biochemical relapse (BCR)-free survival of PCa patients according to the expression levels of eIF3m in GSE70770 cohorts (n=101 for the low group, n=102 for the high group; Log-rank test). H) The Forrest plot demonstrates potential prognostic factors for BCR-free survival in GSE70770 cohorts. Cox proportional hazards regression models were used. *p<0.05, ***p<0.001

eIF3m regulates c-Myc expression in PCa. As we have demonstrated that eIF3m affects c-Myc signaling in PCa, we wonder whether eIF3m could regulate the expression of c-Myc. We measured both protein and mRNA levels of c-Myc in control and eIF3m-depleted PCa cells and observed a decrease in c-Myc expression following eIF3m knockdown at both levels (Figures 5A–5C). Additionally, we explored the correlation between c-Myc and eIF3m in PCa tissues using IHC for protein levels and RNA expression profiles from open-access PCa RNA-seq datasets for RNA levels. The IHC results indicated a positive correlation between c-Myc and eIF3m staining in patient PCa tissues (Figures 5D, 5E). Similarly, a positive relationship between c-Myc and eIF3m was confirmed at the RNA level in patients across three PCa RNA-seq datasets (Figures 5F–5H). Collectively, these data suggest that eIF3m could regulate c-Myc expression.

Discussion

The development and progression of PCa result from the intricate and imbalanced regulation of important oncogenic genes and their related pathways. This abnormal regulation arises from various exterior and internal carcinogenic factors. However, the molecular mechanisms underlying PCa

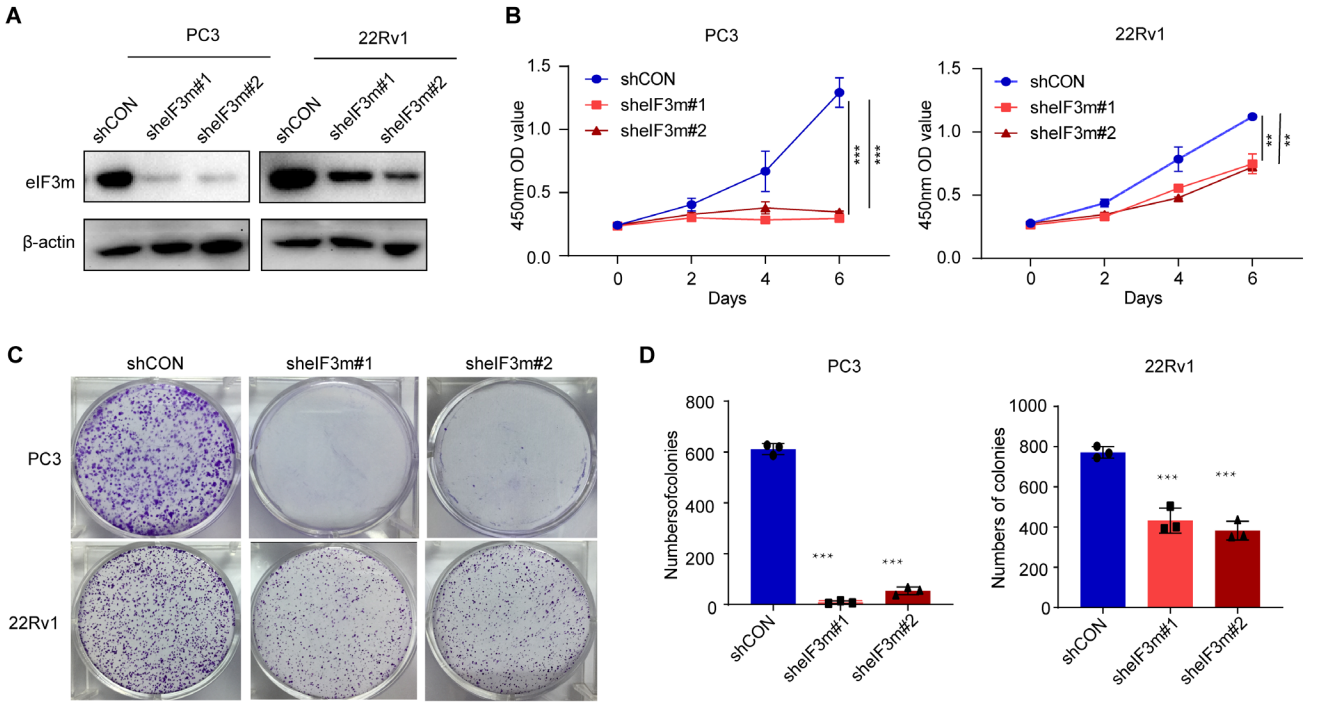

Figure 2. eIF3m knockdown inhibits PCa cell growth *in vitro*. A) The knockdown efficiencies of shRNAs targeting eIF3m were assayed by western blot; β-actin was used as a loading control. B) CCK-8 assay was used to assess the viability of each cell group at the indicated time points. (mean ± SD, n=3, ANOVA). C) Colony formation assay in PC3 and 22Rv1 cells expressing the indicated shRNAs. D) The numbers of colonies in each group were counted (mean ± SD, n=3, ANOVA). ***p<0.001

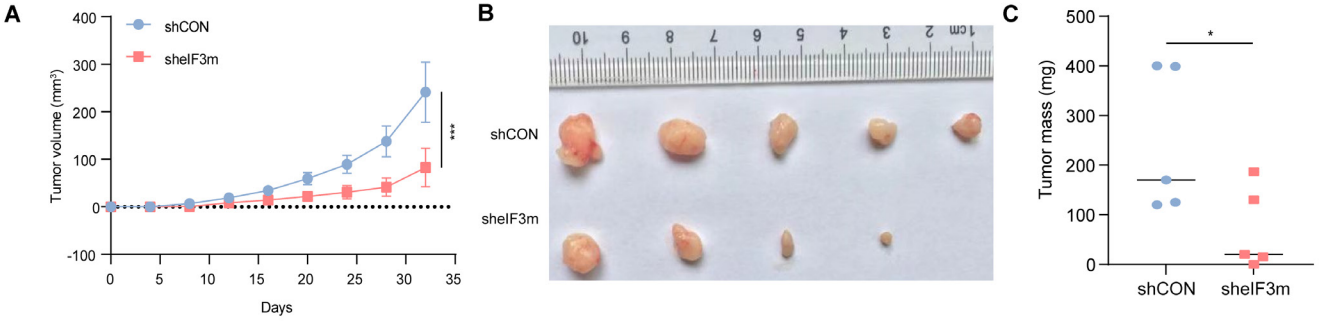

Figure 3. eIF3m is required for PCa cell growth *in vivo*. A) PC3 cells with intact eIF3m expression or eIF3M depletion (5×10^5) were suspended in PBS mixed with Matrigel (volume, 1:1) and subcutaneously implanted into male Balb/c nude mice (n=5). Tumor volume at each time point was documented (ANOVA). B) Mice were sacrificed 32 days later, and the xenografts were pictured. C) The weight of xenografts in each group was measured. Student's t-test. *p<0.05, **p<0.01, ***p<0.001

carcinogenesis remain poorly understood. eIF3, the largest and the most complex translation initiation factor in human cells, plays a critical role in translation and protein synthesis, essential for successful embryonic development and the maintenance of normal tissue homeostasis [31]. However, the functions of eIF3 subunits in cancer, independent of their role in protein translation, are still not fully understood [32]. Various studies have reported their involvement in carcinogenesis [33, 34].

In the present study, we found that eIF3m is abnormally upregulated in PCa tissues in comparison to benign tissues. Higher eIF3m expression indicates shorter recurrence-free survival for patients after radical prostatectomy. Similarly, eIF3m has been reported to be upregulated in several other tumors including lung adenocarcinoma [35], colon cancer [36], and triple-negative breast cancer [37], where eIF3m is aberrantly overexpressed in tumor tissues and elevated eIF3m expression is closely associated with poor clinical outcomes.

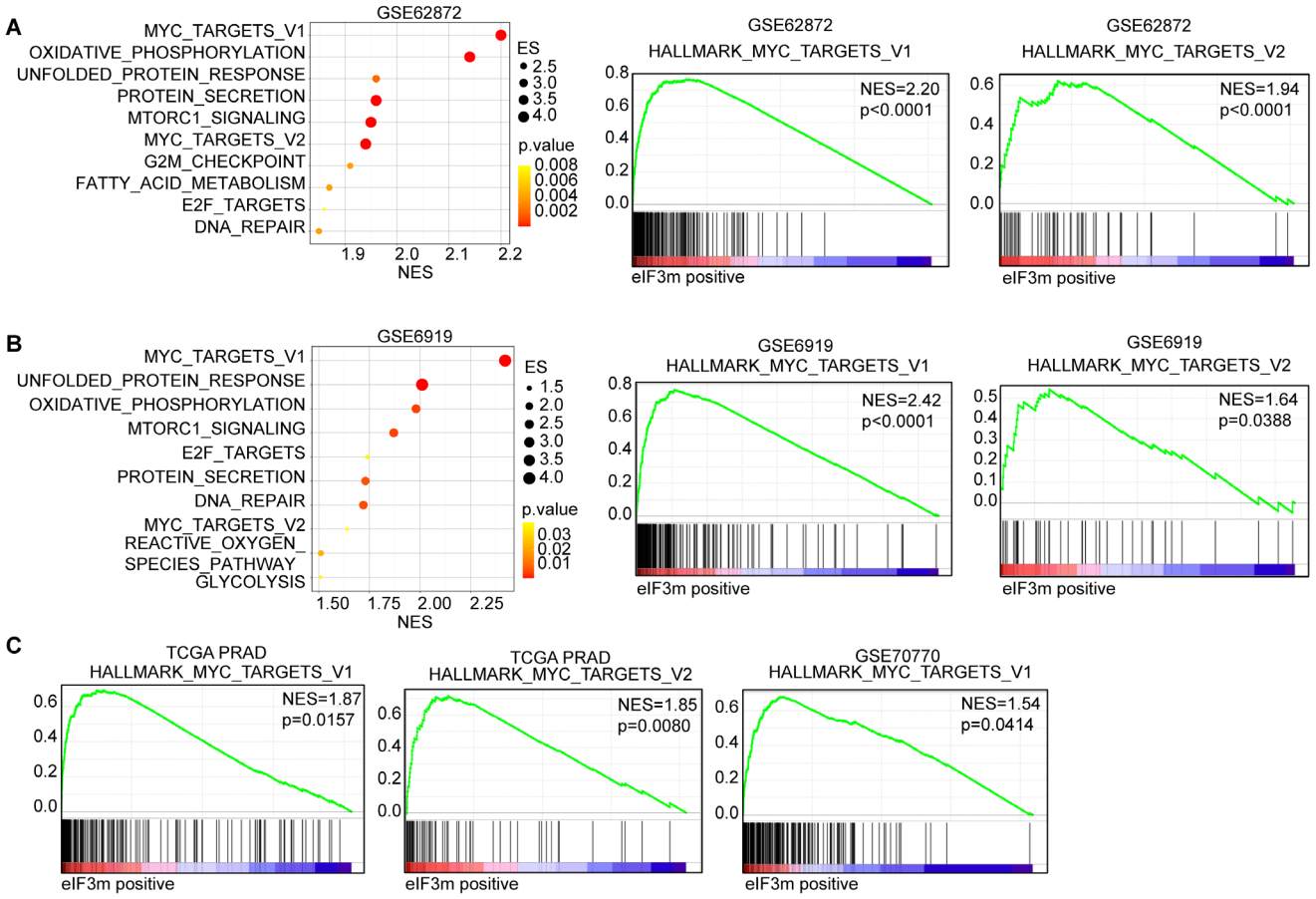

Figure 4. eIF3m affects the activation of c-Myc signaling in PCa. A, B) Gene set enrichment analysis (GSEA) performed based on hallmark gene sets indicated that the c-Myc targets were the top enriched gene set in patients with high eIF3m expression in the indicated PCa cohorts. The results are shown in rank order according to the normalized enrichment score and the p-value. C) The gene set of c-Myc target genes was also enriched in patients with high eIF3m expression in TCGA PRAD and GSE70770 datasets.

These findings, along with our own, support the notion that eIF3m plays an oncogenic role in malignant tumors.

Consistent with our novel discovery of eIF3m's involvement in PCa progression, our *in vitro* and *in vivo* experiments provide strong evidence that silencing eIF3m inhibits the growth of PCa cells. Other reports also have demonstrated that eIF3m could enhance the malignant phenotype of various cancers. For example, eIF3m knockdown suppresses cell proliferation and cell cycle progression while inducing cell death in human colon cancer cells [36]. In lung adenocarcinoma, eIF3m binds to the 5'UTR of CAPRIN1 and positively regulates its expression, promoting proliferation and migration [35]. Additionally, in triple-negative breast cancer, targeting eIF3m inhibits cell proliferation, migration, and invasion, while enhancing apoptosis and decreasing mitochondrial membrane potential in breast cancer cells [37]. Therefore, targeting eIF3m may represent a promising strategy to impede PCa progression.

Our findings that eIF3m regulates the proliferation of PCa cells and correlates with PCa progression drive us to identify the key oncogenic signaling pathways mediating these effects. Through the GSEA analysis in several PCa cohorts, we discovered that c-Myc-regulated gene sets rank among the top hallmarks positively correlated with eIF3m. Further exploration revealed that silencing eIF3m inhibits c-Myc expression at both the RNA and protein levels. eIF3m is known to regulate gene expression by binding the 5'UTR of target mRNAs [35] and may also influence ribosome biogenesis and transcription [30]. In colon cancer, eIF3m regulates the mRNA expression of MIF and MT2, promoting cell cycle progression [36]. Thus, eIF3m likely enhances c-Myc expression at the RNA level, facilitating PCa progression. Notably, our study identified a coordinated upregulation of both eIF3m and c-Myc in clinical PCa samples, further underscoring the pathological significance of eIF3m in regulating c-Myc during PCa progression.

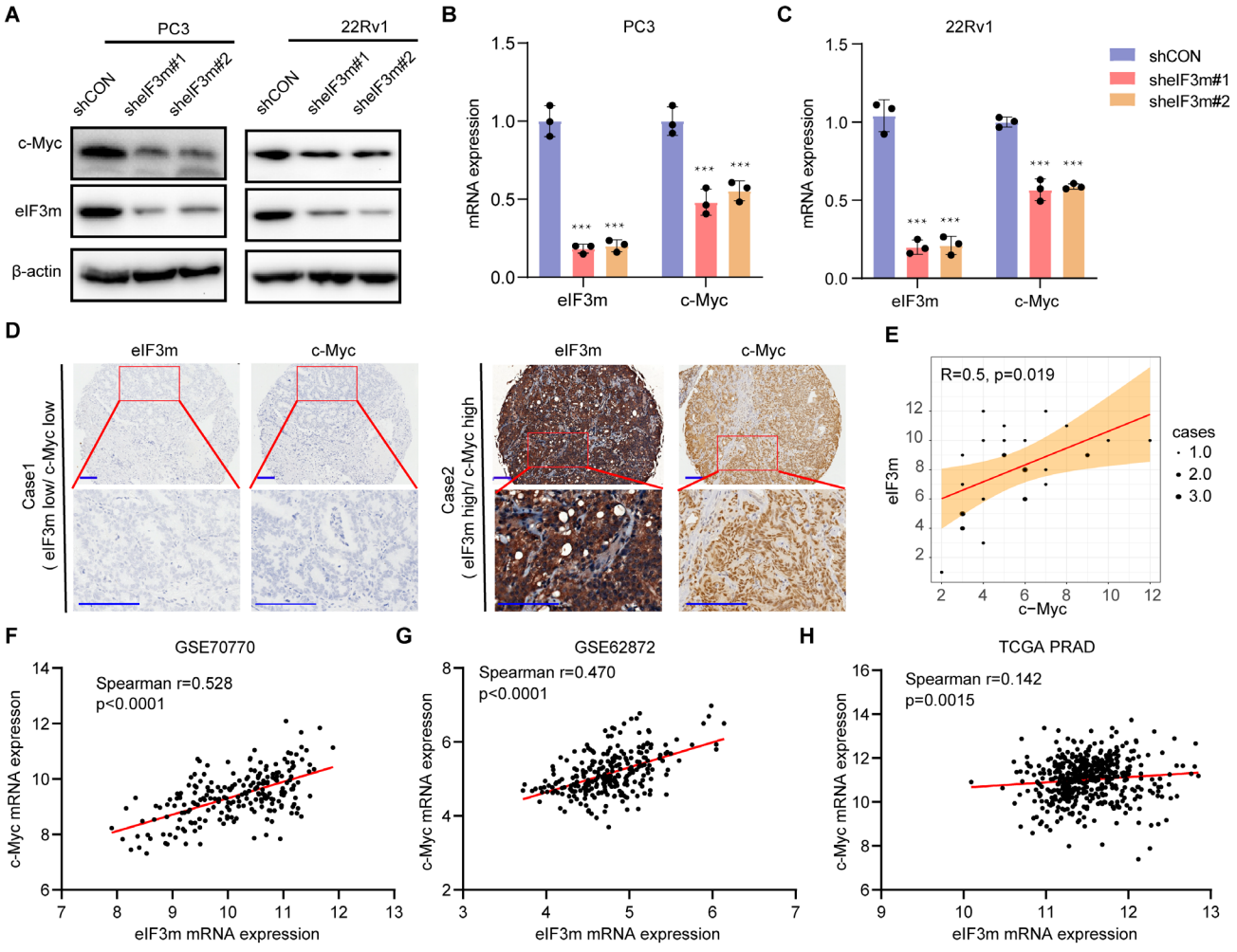

Figure 5. eIF3m regulates c-Myc expression in PCa. A) The protein levels of c-Myc and eIF3m were measured by western blot in PCa cells with or without eIF3m knockdown. β-action was used as a loading control. B, C) The mRNA expression of c-Myc and eIF3m were assayed by qPCR in PCa cells with or without eIF3m knockdown. (mean ± SD, n=3, ANOVA). D) c-Myc and eIF3m were stained in PCa tissues by IHC. E) Correlation between eIF3m and c-Myc expression in PCa samples was analyzed (n=30, Spearman). F–H) The relationship between eIF3m mRNA expression and c-Myc mRNA expression was explored using mRNA profiles from PCa patients accessed from public data sets including (F) GSE70770, (G) GSE62872, and (H) TCGA.

c-Myc is a critical driver gene in PCa, frequently amplified and overexpressed in both early and metastatic stages, and associated with poor survival outcomes [4, 15]. c-Myc signaling regulates various aspects of tumor biology, including proliferation, cell cycle, metastasis, and immune evasion [38]. For example, scRNA-seq studies show that c-Myc promotes PCa metastasis and enhances the expression of immune checkpoints such as PD-L1 and CD47 [39], while also reprogramming the tumor microenvironment during PCa progression [40, 41]. Moreover, c-Myc overexpression antagonizes the canonical AR transcriptional program, contributing to tumor initiation and progression [42]. Our findings indicate that eIF3m regulates c-Myc expression and signaling, highlighting eIF3m's significant role in promoting PCa progression. Recent studies have identified new regulators of c-Myc in PCa, such as RNA helicase DDX52, which enhances c-Myc expression to promote cell growth [43], and USP16, a deubiquitinating enzyme that stabilizes c-Myc protein [44]. Additionally, receptor-interacting protein kinase RIPK2 modulates c-Myc stability and activity [45]. Our research introduces eIF3m as a new regulator of c-Myc signaling to promote the progression of PCa.

In conclusion, our study demonstrates that eIF3m acts as a promoting factor in PCa progression. eIF3m knockdown could significantly inhibit PCa cell growth and suppress c-Myc expression at both RNA and protein levels. However, the precise mechanism through which eIF3m regulates c-Myc remains to be elucidated. Our findings provide a founda-

tion for exploring the detailed mechanisms by which eIF3m regulates c-Myc and advances PCa progression, emphasizing the potential therapeutic significance of targeting eIF3m in future studies.

Acknowledgments: This study was supported financially by the Natural Science Foundation of China (81972370).

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