ETS transcription factor ELK3: Molecular insights and translational horizons in cancer (Review)

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Abstract. Tumorigenesis is a complex multistage process, with its primary regulatory mechanisms involving the interplay of genetic alterations, immune dysfunction and metabolic abnormalities. Transcription factors serve a crucial role in gene expression regulation, participating in various tumor behaviors such as proliferation, metastasis, angiogenesis and drug resistance. Notably, the abnormal activity of transcription factors is closely associated with cancer initiation and progression, and can promote tumor growth, invasion and therapeutic resistance by regulating angiogenesis, epithelial-mesenchymal transition and metastasis-related gene expression. ELK3 belongs to the ETS transcription factor family and the ternary complex factor subfamily. ELK3 participates in multiple molecular biological processes, and is associated with the initiation, progression, invasion and metastasis of various tumors. The present review summarizes the latest research on the structure of ELK3 and its regulation in normal and tumor tissues, focusing on its primary functions in tumors and the signaling pathways involved. Additionally, the diagnostic value of ELK3 as a biomarker and its potential as a target for tumor-specific therapy are explored.

Contents

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1. Introduction

Cancer is a complex disease accompanied by the collapse of regulatory networks governing cellular proliferation, apoptosis, differentiation, metabolism and immunity. Essentially, aberrant gene expression drives dysregulated cell proliferation and differentiation, endowing cells with the capacities for unlimited proliferation, invasion and metastasis (1). The regulation of gene expression relies on interactions among numerous factors, the synergistic effects of which generate cell- and tissue-specific expression patterns. Transcription factors are downstream mediators of cancer regulatory pathways and are a diverse group of proteins that function to either suppress or activate target genes. During tumor progression, dysregulation of transcription factors with oncogenic or tumor-suppressive functions triggers multiple biological behaviors in tumor cells, including uncontrolled proliferation (2).

Research has indicated that the ETS transcription factor family participates in numerous molecular biological processes, including regulation of the cell cycle, proliferation, differentiation, migration, apoptosis and angiogenesis (3,4). Abnormal expression of ETS transcription factors often leads to disease onset, including tumors, immune dysfunction and neurodegenerative disorders (3,5,6). The ETS transcription factor family is one of the largest transcription factor families, with c-ets-1serving as its prototype. Notably, v-ets was first identified in 1983 by Leprince *et al* (7) as a fusion protein expressed by avian retrovirus E26. Subsequently, homologous genes were identified based on their specific ETS domains, with 29 found in humans, 28 in mice, 10 in nematodes and 9 in fruit flies (8). The highly conserved ETS domain comprises 85 amino acids forming three α-helices and four β-sheets; it adopts a wing-helix-turn-helix topology with the sequence α1-β1-β2-α2-α3-β3-β4, and is typically located at the C-terminus of ETS family transcription factor proteins. This structure enables highly specific recognition and binding to

DNA binding sites containing the 5'-GGA(A/T)-3' sequence, thereby regulating the expression of downstream genes. A study on the human ETS transcription factor family have identified 12 subfamilies through multiple sequence alignment to determine ETS domain homology (9). These include: ETS, ERG, PEA3, ETV2, TCF, GABP (GABPA), ERF, ELF, TEL, ESE, SPI and PDEF (SPDEF). Additionally, 12 ETS transcription factor proteins harbor a PNT domain at their N-terminus; this highly conserved domain comprises four α-helices and one short α-helix or 310-helix formed by 65-80 amino acids, creating a specialized structure that enables interactions with other proteins. Research has indicated that ETS family participates in numerous molecular biological processes, including regulation of the cell cycle, proliferation, differentiation, migration, apoptosis and angiogenesis (3,4). Abnormal expression of ETS transcription factors often leads to disease onset, including tumors, immune dysfunction and neurodegenerative disorders (3,5,6).

The ETS transcription factor ELK3, also known as serum response factor (SRF) accessory protein 2 (SAP2), is encoded by a gene located on chromosome 12 (12q23.1). The encoded protein comprises 407 amino acids with a total molecular weight of 44,240 Da. Research has indicated that ELK3 functions as a transcription repressor, but it can be phosphorylated by Ras and MAPKs, thereby acquiring transcriptional activation activity. Due to its structural specificity, ELK3 undergoes alternative splicing to produce three distinct protein isoforms, each performing different biological functions. It has been indicated that ELK3 serves a crucial role in normal physiological processes, such as growth and development, tissue repair and inflammatory responses (10). In tumors, including pancreatic, breast, prostate colorectal, and liver cancer, ELK3 notably influences biological characteristics, such as tumor cell proliferation, metastasis, angiogenesis, microenvironmental regulation and chemotherapy resistance (11-20). The present review summarizes advances in ELK3 research, elucidating its specific mechanisms influencing tumor progression, and explores its potential as a molecular target for cancer therapy.

2. Function and structure of the ELK3 protein

ELK3 (also known as NET and SAP2) belongs to the subfamily of ternary complex factors (TCFs), other members of which include ELK1 and ELK4 (SAP-1). Sequence alignment has revealed that the TCF subfamily shares four similar A-D domains (Fig. 1). The N-terminal A domain corresponds to the ETS DNA-binding domain, which enables this subfamily to function as a transcriptional repressor by recruiting transcriptional repressors and DNA-binding inhibitors. The B domain can form a ternary nuclear protein complex with SRF, a member of the MADS-box transcription factor family, on the serum response element (SRE) of c-fos (3,18) (3,21). The C-terminal C domain contains multiple S/TP MAPK phosphorylation sites, enabling activation through MAPK phosphorylation. The D domain serves as the MAPK and ELK3 nuclear localization signal linker site. Additionally, TCF subfamily proteins possess an extra MAPK linker site, the F domain, which exhibits distinct binding characteristics from the D domain. Notably, beyond these shared domains, each gene contains unique regions conferring distinct biological functions. Specifically, the ELK1 protein contains an R-motif between domains B and D that inhibits domain C activity. The ELK3 protein possesses two inhibitory domains: The NET inhibitory domain (NID) and the C-terminal binding protein inhibitory domain (CID). The ELK4 protein (SAP-1a) also harbors an NID domain between domains B and D (22).

Current research suggests that ELK3 functions as a transcriptional repressor. Potential mechanisms include: NID interacting with Ubc9 and PIAS1, leading to increased acetylation at lysine 162; and CID interacting with the C-terminal binding protein of the E1A corepressor, which inhibits transcription via histone deacetylase activity (23-25). Notably, reports have indicated that growth factors and Ras genes can induce MAPK signaling, leading to phosphorylation and activation of key residues in the C-domain of ELK3 by ERK and p38, thereby triggering transcriptional activation (24-26). Alternative splicing is a crucial post-transcriptional and co-transcriptional mechanism for gene expression regulation, enabling the production of multiple mature mRNA transcripts from a single gene to generate substantial transcript and proteome diversity (27). Three additional ELK3 protein isoforms, ELK3b, ELK3c and ELK3d, have been identified. ELK3b and ELK3c possess only the N-terminal A domain, B-box and NID, lacking the C domain, D domain and CID (28,29).The ELK3d isoform possesses a truncated ETS DNA-binding domain (lacking the predicted β3 and β4 strands) while retaining most of the transcription activation domain. It lacks the transcription repression domains NID and CID, but can activate transcription via ETS binding sites (28). ELK3d also retains four of the five C-terminal Ser/Thr-Pro motifs (Thr 337, Ser 359, Ser 365 and Ser 398) and the F domain from ELK3, which may explain the transcriptional activation activity of ELK3d (26).

Alternative splicing events drive the translation of ELK3 into functionally distinct protein isoforms, which may exhibit markedly divergent biological activities and modes of action. To the best of our knowledge, no studies to date have elucidated the physiological and pathological functions of individual ELK3 isoforms. Direct experimental evidence in this research field remains absent, indicating an urgent need for systematic *in vitro* and *in vivo* investigations to identify their biological roles.

3. ELK3 expression and prognostic impact in tumors

Reports have indicated that ELK3 not only exhibits abnormal expression in multiple tumors but that it is also associated with tumor prognosis. The present review examined ELK3 expression across 34 tumor types using the Sangerbox online analysis platform [Data source: The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET) and GTEx]. Abnormal ELK3 expression was observed in 27 tumor types, with high expression detected predominantly in solid tumors, and low expression observed in uterine corpus endometrial carcinoma, breast invasive carcinoma, kidney renal papillary cell carcinoma, prostate adenocarcinoma, lung squamous cell carcinoma, adrenocortical carcinoma and kidney chromophobe (Fig. 2). Furthermore, multiple experimental studies have suggested dysregulation of ELK3 expression in cancer. For example,

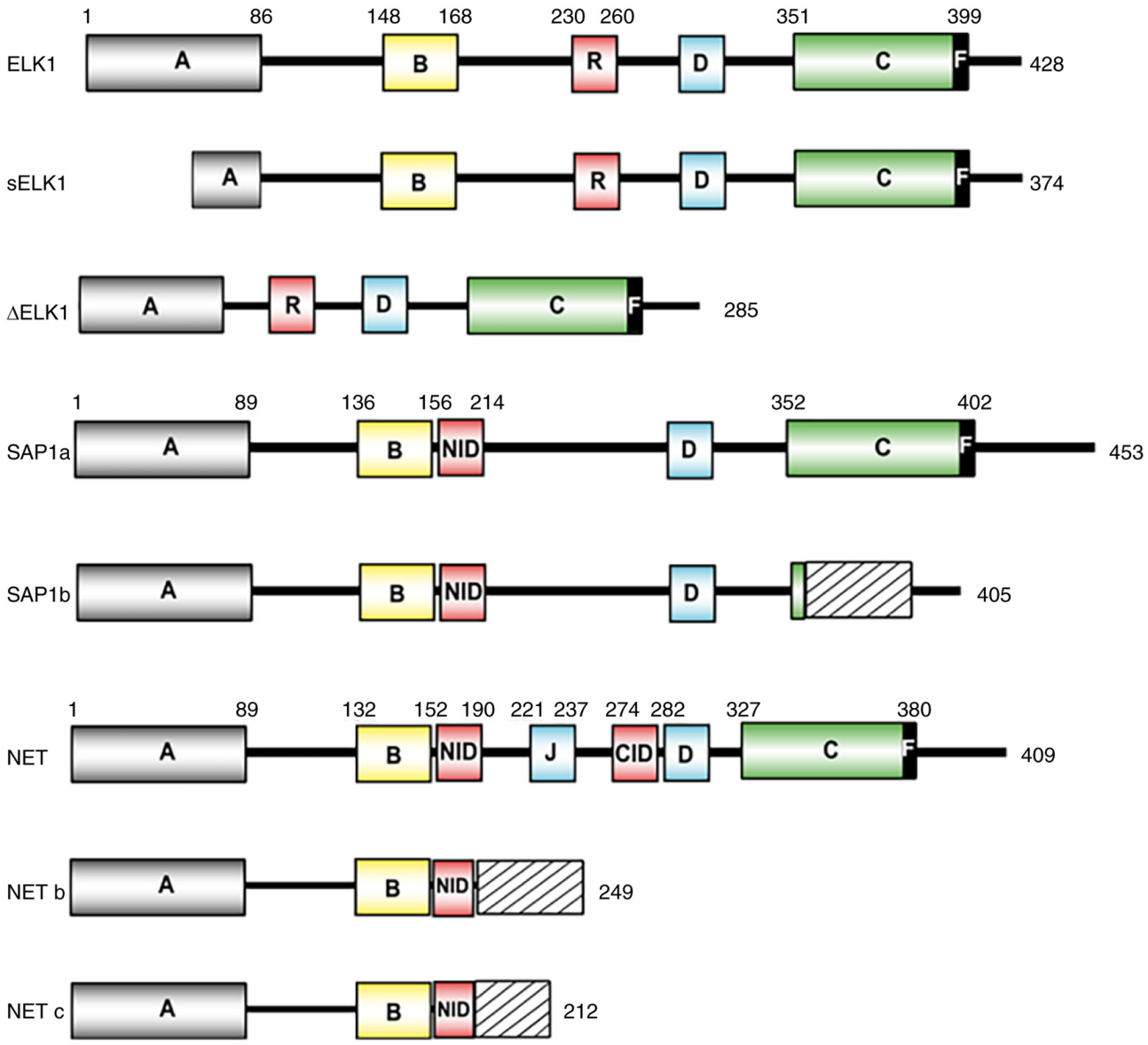

Figure 1. Structure of the ternary complex factor subfamily. ELK1 protein isoforms: Elk1, sElk1 and ΔElk1. ELK4 protein isoforms: Sap1a and Sap1b. ELK3 protein isoforms: Net, Net b and Net c. Figure adapted with permission from (22). CID, C-terminal binding protein inhibitory domain; NID, NET inhibitory domain; SAP, serum response factor accessory protein.

Liu *et al* (13) reported that ELK3 expression was markedly elevated in glioma and was increased in higher World Health Organization grades, and that patients with high ELK3 expression exhibited a poor prognosis. Subsequent studies have confirmed these findings (30,31). Zhao *et al* (14) identified that high ELK3 expression in 70 pancreatic cancer samples predicted poorer overall prognosis. Cheng *et al* (32) similarly confirmed this association in pancreatic cancer. An immunohistochemical study of 45 gallbladder cancer cases showed significantly higher ELK3 protein expression in neoplastic tissue compared with in adjacent non-neoplastic tissue, and patients with ELK3-positive expression had a lower 3-year overall survival rate than the negative expression group (33). In a study on cervical cancer, ELK3 protein expression levels were revealed to be markedly higher in tumor tissue than in adjacent non-neoplastic tissue, and its expression was associated with poor overall survival (34). Wang *et al* (35) used bioinformatics analysis to validate the upregulation of ELK3 as an independent prognostic factor in ovarian cancer. In our previous studies, analysis of multiple datasets revealed markedly higher ELK3 expression in gastric cancer compared with in adjacent non-cancerous tissue, predicting a poor prognosis in patients with gastric cancer (36,37). A subsequent study by Wang *et al* (38) in gastric cancer was consistent with our prior findings. These studies collectively indicate abnormal upregulation of ELK3 in tumors, potentially promoting malignant progression. However, studies in pleural mesothelioma have detected low ELK3 expression (18,39). Moreover, contradictory conclusions exist within the same tumor type. For example, Heo *et al* (12) demonstrated higher ELK3 expression in breast cancer cell lines compared with in normal breast cell lines, whereas He *et al* (40) reported downregulation of both RNA and protein expression levels of ELK3 in primary breast cancer specimens. ELK3 prognostic data from 44 tumors in the Sangerbox online analysis platform (Data source: TCGA and TARGET) indicated that high ELK3 expression may be

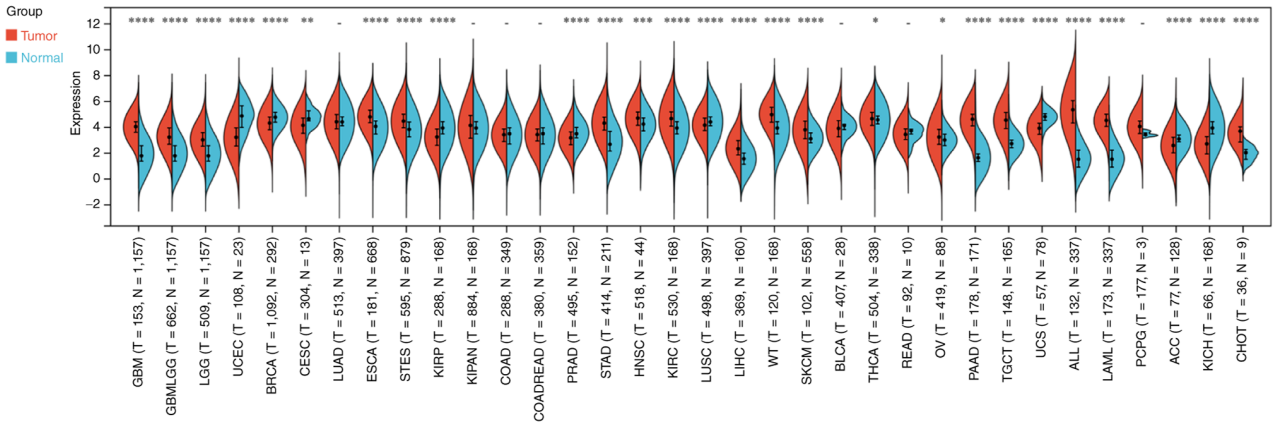

Figure 2. Expression of ELK3 in different tumors. Uniformly standardized pan-cancer datasets (TCGA, TARGET and GTEx) were downloaded from the UCSC Xena database (https://xenabrowser.net/). The expression data of the ELK3 gene across all samples were extracted from these datasets. All expression values were subjected to log2(x+0.001) transformation. Subsequently, cancer types with fewer than three samples were excluded, and expression data covering a total of 34 cancer types were retained. Unpaired Wilcoxon rank-sum tests were applied to analyze the statistical significance of expression differences. *P<0.05, **P<0.01, ***P<0.001, ****P<0.001. N, normal; T, tumor.

associated with a poor prognosis in 14 tumors (glioblastoma and lower grade glioma, brain lower grade glioma, stomach adenocarcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, sarcoma, glioblastoma multiforme, mesothelioma, kidney renal papillary cell carcinoma, lung squamous cell carcinoma, acute myeloid leukemia, the combined dataset of stomach and esophageal carcinoma, bladder urothelial carcinoma and ovarian serous cystadenocarcinoma), whereas its high expression predicted improved prognosis in four tumor types (kidney renal clear cell carcinoma, acute lymphoblastic leukemia, relapsed acute lymphoblastic leukemia and skin cutaneous melanoma) (Fig. 3).

ELK3 exhibits distinct or even opposing biological functions across different tumor types, which may stem from the combined effects of multiple factors: Heterogeneous isoforms derived from alternative splicing, divergent backgrounds of tumor driver mutations, lineage-specific transcriptomic profiles of cells, regulation by the tumor microenvironment (TME), dose-dependent expression effects (for example, ELK3 expression and phosphorylation dictate the magnitude and polarity of its regulation over angiogenesis, tumor invasion and endothelial barrier function.) and tissue-specific post-translational modifications.

4. ELK3 expression regulation

Regulation of gene and protein expression covers six hierarchical layers: Chromatin remodeling, transcription, post-transcriptional processing, mRNA homeostasis, translation and post-translational modification. The expression regulation of ELK3 depends on the interaction among numerous factors, the synergistic effects of which generate cell- and tissue-specific expression patterns; these mechanisms are summarized in Table I.

Transcription initiation regulation. Transcriptional regulation modulates gene expression through tightly coordinated temporal and spatial interactions between transcription machinery (including RNA polymerase II, trans-acting factors and associated cofactors) and regulatory elements on chromosomal DNA (1,41). During the initiation phase of gene transcription, general transcription factors associate with the promoter region of the gene and bind to RNA polymerase II; however, efficient transcription is difficult at this stage (1,2). Transcription factors, also known as trans-acting factors, are proteins that directly or indirectly recognize and bind to core sequences of specific cis-acting elements. With the assistance of gene-specific transcription factors, they can induce RNA polymerase II to form an effective transcription initiation complex, thereby exerting efficient transcriptional regulation (1). Thus, the variation in gene expression leading to different types of cellular differentiation (such as morphological features, biological functions and proliferative capacity) is largely regulated by transcription factors. For example, Tsoyi *et al* (42) demonstrated that the transcription factor specificity protein 1 binds to the ELK3 promoter to promote its expression. Zinc finger E-box binding homeobox 1 (ZEB1), a zinc finger transcription factor, not only recruits co-repressors or co-activators, but also binds to specific DNA sequences containing E-box elements to regulate target gene expression. In studies of breast and pancreatic cancer, ZEB1 has been shown to directly bind to ELK3 target genes to enhance their expression (14,43). Research by Park and Park (44) revealed that the ELK3 promoter region contains a transcription factor SMAD3 binding site, which can directly activate transcription and increase expression.

Post-transcriptional regulation. Post-transcriptional regulation of gene expression serves a crucial role in various cellular processes, including cell development, metabolism and cancer progression. Immediately after transcription initiates the formation of mRNA precursors, these precursors are enveloped by numerous proteins forming ribonucleoprotein complexes. mRNA-binding proteins associate with nascent mRNA precursors and mediate various RNA processing reactions, ultimately yielding mature mRNA (45). N6-Methyladenine is the most common post-transcriptional modification in

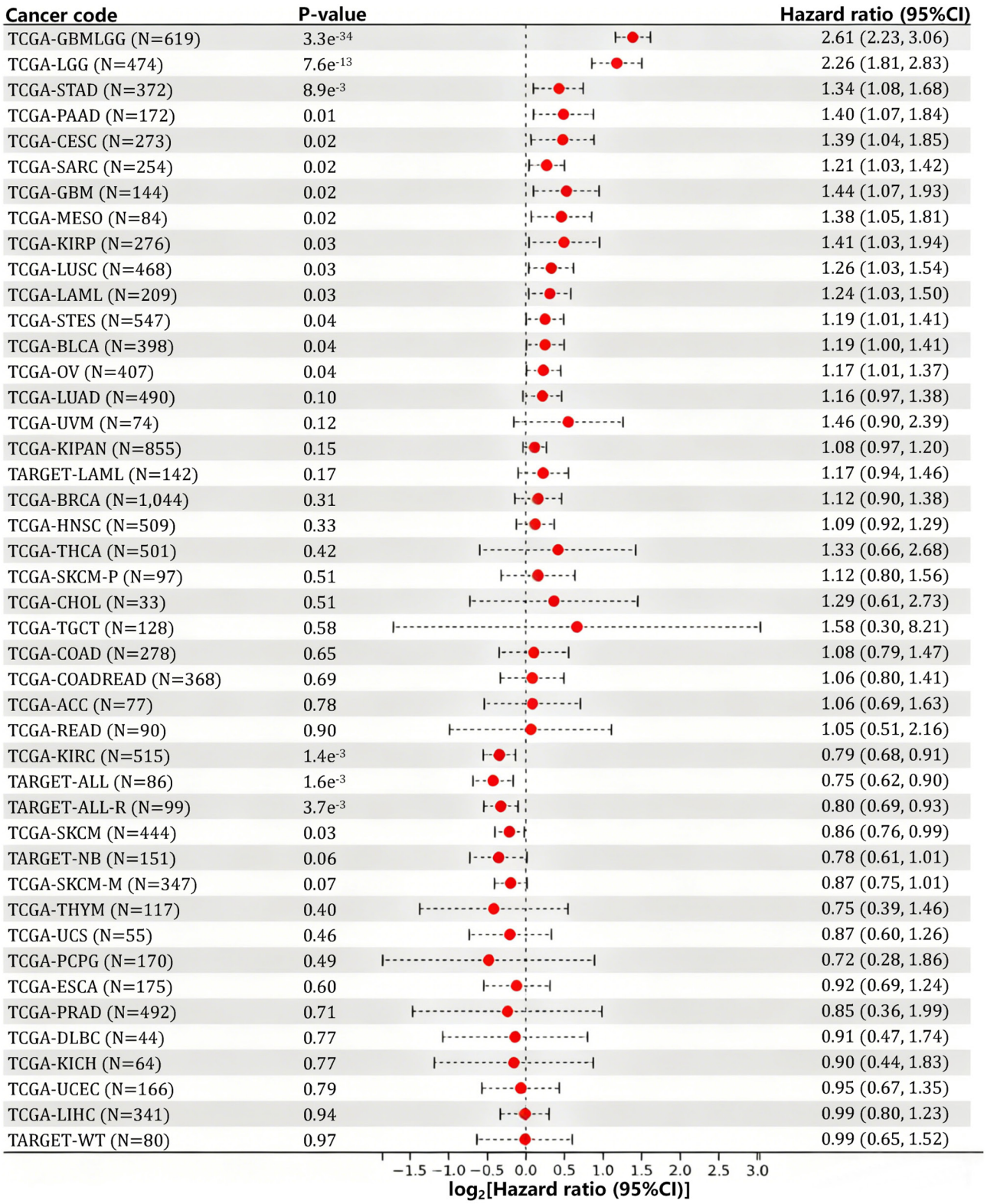

Figure 3. Relationship between ELK3 expression and prognosis in different tumors. TCGA, The Cancer Genome Atlas; TARGET, Therapeutically Applicable Research to Generate Effective Treatments.

eukaryotic mRNA. Methylation modifications in the 5'UTR region of mRNA serve crucial roles in mRNA splicing, editing, stability, degradation and polyadenylation, while methylation in the 3'UTR region facilitates nuclear export, translation initiation and maintains mRNA structural stability in conjunction with polyA-binding proteins (46). Methyltransferase-like protein 11A (METTL11A) binds to the 5'UTR region for methylation. Zhang *et al* (34) demonstrated that METTL11A can promote tumor progression by upregulating ELK3 in cervical cancer. MicroRNAs (miRNAs/miRs) are a class of regulatory, endogenously expressed non-coding small RNA molecules that primarily control mRNA expression by binding

Table I. Mechanisms of ELK3 expression regulation.

A, Transcription initiation regulation			
Regulatory molecule/condition	Regulatory mechanism	Expression alteration	(Refs.)
SP1, SMAD3	Binding to the ELK3 promoter	Upregulation	(2,14,41)
B, Post-transcriptional regulation			
Regulatory molecule/condition	Regulatory mechanism	Expression alteration	(Refs.)
miR-200a, miR-155-5p, miR-135a	Binds to ELK3 mRNA 3'UTR	Downregulation	(43,48,49)
Linc00662/miR-890, Linc00525/miR-507, Linc01106/miR-3612	Competing endogenous RNA	Upregulation	(46,47,50)
METTL11A	N6-methyladenosine	Upregulation	(32)
C, Protein post-translational modification			
Regulatory molecule/condition	Regulatory mechanism	Expression alteration	(Refs.)
Ras/MAPK, RSK2	Phosphorylation	Upregulation	(23,53)
Ubc9, PIAS1, E1A	Acetylation	Downregulation	(23-25)
Hypoxia	Ubiquitination	Downregulation	(51)

METTL11A, methyltransferase-like protein 11A; miR, microRNA; RSK2, ribosomal S6 kinase 2; SP1, specificity protein 1; ZEB1, zinc finger E-box binding homeobox 1.

to the 3'UTR (47). Studies have indicated that miR-507, miR-200a, miR-3612, miR-155-5p, miR-890 and miR-135a suppress ELK3 expression (45,48-52). Based on the mechanism of miRNA-mediated gene suppression, long non-coding RNAs can exert competing endogenous RNA (ceRNA) regulatory functions by competitively binding to shared miRNA sequences and affecting the expression levels of their downstream target mRNA (53). Xia *et al* (52) demonstrated that Linc00662/miR-890 regulates ELK3 expression in melanoma via a ceRNA mechanism. Similarly, Linc00525/miR-507 and Linc01106/miR-3612 regulate ELK3 in colorectal cancer and bladder cancer, respectively.

Post-translational modification (PTM) of proteins. PTM of proteins refers to covalent and generally enzyme-catalyzed modifications occurring after protein biosynthesis. After mRNA is translated into polypeptide chains, PTMs occur to form mature protein products; this process forms the molecular basis for protein dynamic equilibrium and interactions, participating in nearly all biological processes (54). Among PTMs, we have previously demonstrated that acetylation modifies ELK3 to inhibit its transcriptional activity, whereas phosphorylation by Ras promotes its transcriptional activity. Furthermore, Yoo *et al* (55) investigated a novel mechanism of ELK3 phosphorylation in breast cancer, revealing that ELK3 serves as a substrate for ribosomal S6 kinase 2, which phosphorylates ELK3 to mediate its activation. Gross *et al* (56) also demonstrated that ELK3 ubiquitination levels are increased under hypoxic conditions, leading to reduced ELK3 expression (Fig. 4).

5. Biological functions of ELK3 in tumors

Appropriate regulation of gene expression is crucial for normal cellular development. Given that the aforementioned multi-layered regulatory mechanisms exhibit pronounced lineage-specific, tumor microenvironmental and tissue-specific characteristics, they drive aberrant ELK3 expression, thereby facilitating the initiation and progression of diseases such as cancer. Notably, these divergent regulatory patterns result in distinct ELK3 functional phenotypes across various tumor types (Fig. 5).

ELK3 regulates tumor proliferation. Tumor cells exhibit 10 hallmark characteristics, among which the maintenance of chronic proliferation is the most fundamental feature (57). Normal cells are regulated by multiple signals that promote or inhibit proliferation, guiding cells into normal division and growth cycles. This ensures proper cell numbers and morphology, thereby maintaining normal tissue structure and function. By contrast, tumor cells can operate independently of these regulatory signals, acquiring the ability for unlimited proliferation. Research has indicated that ELK3 promotes cell proliferation in multiple tumor types, including glioma, pancreatic cancer, breast cancer and melanoma (12-15,58). Park *et al* (59) demonstrated that ELK3 can promote the tumor-associated lymphatic secretion of exosomes. Exosomes enriched with ELK3 increase the expression of oncogenic miR-30e-3p in tumor cells, while downregulating the expression of tumor-suppressing miR-503-3p and miR-4269, thereby driving breast cancer proliferation (15). ELK3 also regulates

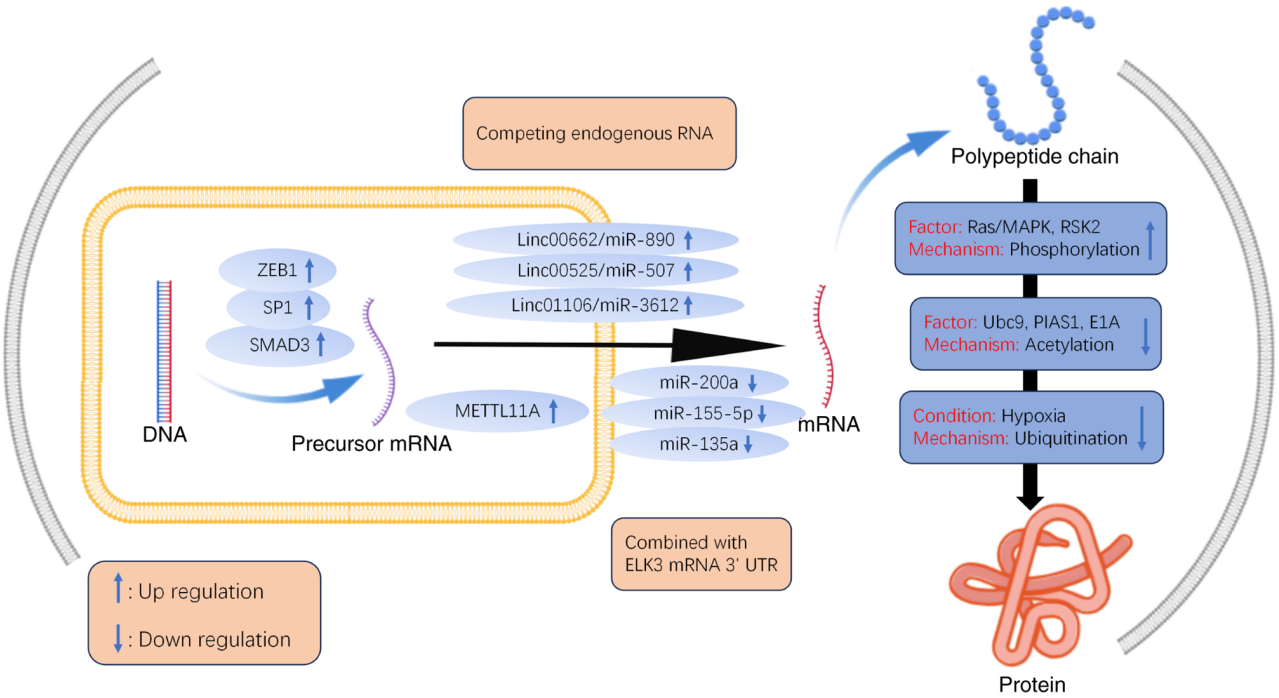

Figure 4. Regulation of ELK3 expression. METTL11A, methyltransferase-like protein 11A; miR, microRNA; RSK2, ribosomal S6 kinase 2; SP1, specificity protein 1; ZEB1, zinc finger E-box binding homeobox 1.

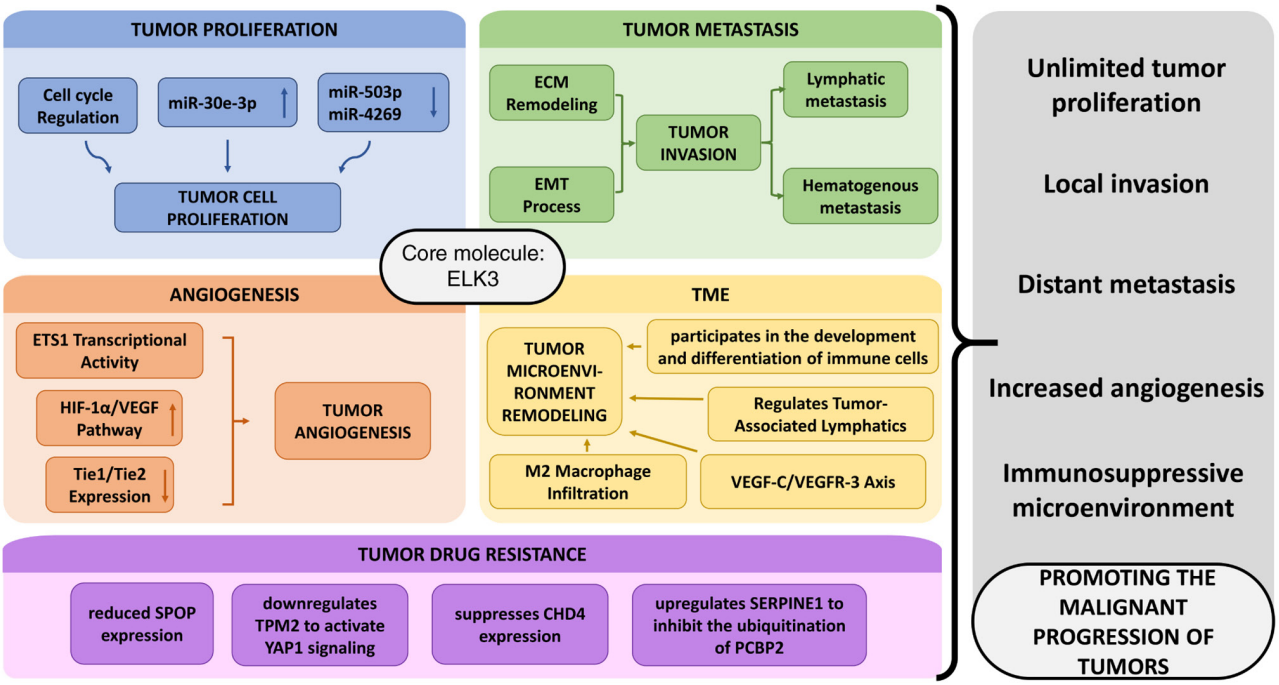

Figure 5. Mechanisms underlying ELK3-mediated regulation of tumor proliferation, metastasis, angiogenesis and the tumor microenvironment. ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; HIF-1α, hypoxia-inducible factor-1α; miR, microRNA; TPM2, tropomyosin-2; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; TME, tumor microenvironment.

the cell cycle, where checkpoints serve as critical control points for proliferation. The G_1-S checkpoint governs cell entry into S phase, the S checkpoint prevents DNA-damaged cells from synthesizing DNA, and the G_2 checkpoint blocks damaged cells from entering mitosis (60). Mao *et al* (16) demonstrated that ELK3 downregulation in prostate cancer cells increased S-phase and G_2-M phase durations by 58 and 62%, respectively, thus promoting tumor proliferation. Activated ELK3 can also bind to SRF and associate with the SRE of the c-fos proto-oncogene, promoting its oncogenic activity (3,21,55). A study on pancreatic cancer demonstrated that ELK3 overexpression suppresses c-fos transcription via its dual

inhibitory domains NID and CID, thereby downregulating c-fos expression and restraining the proliferation of pancreatic cancer cells (61). Whether ELK3 facilitates cell proliferation in pancreatic cancer remains controversial; however, most existing studies generally regard ELK3 as an oncogene that accelerates the proliferation of solid tumors, marking it as a promising biomarker.

ELK3 regulates tumor metastasis. Metastasis represents another critical tumor characteristic, and a primary cause of treatment resistance and mortality. Tumor cell dissemination primarily occurs via two pathways: Lymphatic invasion, where cells infiltrate lymph nodes and drain to distant organs; and hematogenous spread, where cells circulate through the bloodstream to distant sites such as the liver, brain, bone or lungs. Abnormal expression of genes associated with tumor metastasis often enhances metastatic potential. Studies have confirmed that ELK3 influences cell metastasis in multiple tumor types (12,14,16-20,62,63). For example, Sloan *et al* (17) demonstrated that ELK3 may affect caveolin-1 transcription in lung cancer, thereby altering cancer cell metastatic capacity. Choi *et al* (64) demonstrated that ELK3 regulates ID4 promoter activity, and the ELK3-ID4 axis modulates metastatic properties in triple-negative breast cancer cells. Additionally, it has been indicated that ELK3 promotes ovarian cancer cell migration and invasion by targeting AEG1 (65).

Moreover, inhibiting tumor metastasis is notably more challenging than suppressing tumor cell proliferation, as metastasis involves a number of complex interactions between tumors and the extracellular matrix (ECM). The ECM comprises diverse proteins, including collagens, glycoproteins and secreted proteins, which interact with cells and transmit extracellular signals, thereby altering cellular phenotypes (66). ECM remodeling alters the TME, leading to metastasis (67). In gastric cancer, Lee *et al* (18) reported that ELK3 promotes cancer cell spread by regulating the expression of ECM remodeling-related genes, such as bone morphogenetic protein 1 and lysyl oxidase-like 2. Lee *et al* (18) also demonstrated that inhibiting ELK3 can accelerate tumor cell metastasis by modulating the expression of genes associated with ECM remodeling, such as bone morphogenetic protein 1 and lysyl oxidase-like 2. Furthermore, the adhesion of tumor cells to the matrix serves a crucial role not only in cell proliferation, but also markedly contributes to the process of tumor metastasis. In breast cancer, ELK3 may act as a transcriptional activator for MT1-MMP gene expression, degrading multiple ECM components (12). Conversely, Mao *et al* (16) demonstrated that decreased ELK3 expression upregulates serpin family E member 1, which binds to MMPs to mediate ECM degradation; this reduces prostate cancer cell adhesion to the matrix, thereby promoting metastasis.

Further studies have indicated that ELK3 mediates epithelial-mesenchymal transition (EMT) (68,69). Li *et al* (70,71) demonstrated that interfering with ELK3 expression inhibits EMT in hepatocellular carcinoma cells. EMT is a critical cellular process that induces polarized epithelial cells to adopt a mesenchymal phenotype, enhancing cell motility. Cancer cells undergo EMT to detach from the primary tumor and disseminate into the bloodstream, leading to metastasis. The loss of E-cadherin, which disrupts intercellular junctions and promotes cell separation, serves as a key biomarker for EMT (72). In breast cancer research, ELK3 has been shown to suppress GATA3 expression through epigenetic mechanisms, and GATA3 promotes E-cadherin transcription (19,20). Cho *et al* (43) demonstrated that ELK3 directly regulates E-cadherin, and revealed that ZEB1 binds to the C-domain of ELK3, forming a protein complex that inhibits ELK3 phosphorylation activity, thereby suppressing E-cadherin expression at the transcriptional level.

EMT is driven by multiple transcription factors, which regulate the expression of classic EMT markers. These transcription factors are initiated and controlled by pathways including TGF-β signaling, Wnt/β-catenin signaling and hypoxia-inducible factor (HIF)-1α (73). Studies in pancreatic and breast cancer have demonstrated that inhibiting ELK3 affects Wnt/β-catenin and TGF-β signaling-induced EMT in tumor cells; however, the precise mechanisms remain unclear (14,19,20,74). Additionally, research has confirmed that ELK3 maintains the invasive and metastatic capabilities of liver cancer stem cells by regulating HIF-1α (75). Research by Gross *et al* (76) indicated that ELK3 may partially participate in prolyl hydroxylase domain (PHD) protein degradation via the E3 ligase SIAH2. PHD proteins serve as primary regulators of HIF-1α, hydroxylating HIF-1α based on intracellular oxygen levels and enabling its recognition by the E3 ligase VHL for degradation (76). In summary, ELK3 facilitates the metastasis of solid tumors by modulating ECM degradation, directly or indirectly regulating EMT, and sustaining the stemness of tumor cells.

ELK3 regulates angiogenesis. Angiogenesis is critical for biological processes such as proliferation and development, with new blood vessels emerging from existing capillaries. In adult mammals, dysregulated angiogenesis is frequently associated with the progression of various diseases, including tumors (77). Using *in situ* hybridization, Ayadi *et al* (78) detected ELK3 expression in sites of angiogenesis and vasogenesis within mouse bladder vessels, cardiac endothelium and the dorsal aorta, providing evidence of its involvement in vascular development. Angiogenesis comprises three steps: Endothelial cell activation, endothelial cell proliferation and migration, and maturation of newly formed vessels. The transition of endothelial cells to an angiogenic phenotype is induced by soluble factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). One of the most potent activators is VEGF, an endothelial cell-specific mitogen that serves a central role in neovascularization (79). Molecular studies by Mou *et al* (80) revealed that ELK3 enhances VEGF-A expression and secretion by promoting HIF-1α ubiquitination and degradation, ultimately promoting glioma angiogenesis. *In vivo* and *in vitro* studies by Zheng *et al* (81) demonstrated that Ras can phosphorylate ELK3, leading to increased activity in the VEGF promoter region (-80 to -53) and elevated expression, indicating its decisive role in angiogenesis. Conversely, Heo *et al* (82) observed that VEGF may influence ELK3 expression at the protein level, potentially through modulating MAPK signaling activity. FGF-2 can also induce ELK3 phosphorylation via an ERK-1/2-dependent pathway, converting ELK3 into an activator of angiogenesis (81). An additional report has indicated that VEGF expression exhibits no marked changes in retinal vessels in ELK3-knockout mouse

models, whereas the RNA expression levels of Tie receptors for angiopoietin, Tie1 and Tie2, are markedly reduced. It was subsequently revealed that Tie2 expression gradually recovers to normal levels with mouse growth, whereas Tie1 expression remains downregulated; this may reflect the involvement of ELK3 in the transcriptional regulation of Tie1 (83). The aforementioned studies collectively demonstrate that ELK3 promotes angiogenesis. However, an *in vitro* study has also suggested that ELK3 recruits the co-repressor Sin3A to inhibit ETS1 activity, leading to dysregulation of MT1-MMP transcription and reduced angiogenic capacity in human umbilical vein endothelial cells (84). Although this contradicts the other findings, based on the mechanism of ELK3 activation, this discrepancy may arise from variations in specific experimental conditions and cell types affecting ELK3 function.

ELK3 regulates the TME. The cellular environment surrounding tumor cells is termed the TME, which is composed of cellular and non-cellular components. These primarily include diverse types of stromal cells (tumor-associated fibroblasts, lymphocytes, macrophages and endothelial cells), immune cells (for example, T and B lymphocytes) and extracellular components (including cytokines, growth factors, hormones and ECM components). These elements envelop tumor cells and are nourished by the surrounding tumor vasculature. Matrix cells within the TME promote tumor growth by directly activating growth signals in tumor cells or remodeling the surrounding area through the release of various molecules (85). Concurrently, they enhance critical biological processes such as tumor heterogeneity, adaptability and evasion of immune surveillance (86-89). Consequently, cells within the TME have emerged as targets for effectively suppressing cancer. Tumor-associated lymphatic vessels (TALVs), composed of lymphatic endothelial cells, constitute a major component of the TME; due to their higher permeability compared with blood vessels, TALVs serve a particularly crucial role in tumor dissemination and metastasis (90). Research by Kim *et al* (15) demonstrated that ELK3 promotes the viability of tumor-associated lymphatic endothelial cells and enhances their capacity to stimulate breast cancer proliferation. Furthermore, Wang *et al* (38) revealed through bioinformatics analysis that the abnormally high expression of ELK3 in tumor cells is closely associated with the VEGF-C/VEGF receptor (VEGFR)-3 axis. Conversely, Park *et al* (59) reported that suppressing ELK3 expression in TALVs can lead to decreased VEGFR-3 expression. The protein encoded by VEGF-C promotes angiogenesis and endothelial cell proliferation by binding to and activating VEGFR-2 and VEGFR-3. Oh *et al* (91) explored the potential mechanism by which ELK3 regulates the VEGF-C/VEGFR-3 axis. ELK3 was shown to induce elevated levels of phosphorylated and acetylated NF-κB in lymphatic endothelial cells, which may subsequently promote upregulation of VEGFC expression. Furthermore, ELK3 expression in gastric cancer has been reported to promote the infiltration of tumor-associated M2 macrophages (38). Macrophages are the most abundant infiltrating immune cells in the TME, participating in tumor cell aerobic glycolysis, proliferation and other biological processes that drive malignant progression. However, the mechanism by which ELK3 regulates macrophages remains unclear.

The majority of current investigations into ELK3-mediated regulation of the TME center primarily on the mechanisms underlying ECM remodeling, lymphangiogenesis and angiogenesis. However, Yang *et al* (92) reported that ELK3 participates in the development and differentiation of immune cells, and a previous study indicated that ELK3 is a key regulator of natural killer (NK) cell therapy response in triple-negative breast cancer (93). Highly expressed in triple-negative breast cancer, ELK3 acts as a core regulator by modulating mitochondrial dynamics to influence NK cell cytotoxicity; knocking down ELK3 has been shown to enhance NK cell antitumor activity (94). Jung *et al* (95) further elucidated the molecular mechanism of ELK3-based immunotherapy. Depletion of ELK3 was shown to increase CXCL16 expression, which in turn can mediate chemotaxis to recruit NK cells, thereby amplifying NK cell cytotoxicity. This process ultimately enhances the antitumor immune response, further solidifying ELK3 as a potential therapeutic target for TNBC (95).

ELK3 regulates tumor drug resistance. Chemotherapy resistance in tumor cells leads to cancer recurrence and metastasis, constituting a notable factor affecting the quality of life and clinical prognosis of patients with cancer, and a major obstacle in cancer treatment. Current molecular mechanisms of tumor chemotherapy resistance include abnormal activation of ABC transporters, mitochondrial alterations, DNA repair, autophagy, EMT, cancer stemness and exosomes (96). Wang *et al* (38) demonstrated that high ELK3 expression counteracts the anticancer effects of axitinib. In a clinical study, Lee *et al* (97) revealed that elevated ELK3 levels in prostate cancer tissues leads to decreased SPOP expression. Docetaxel induces cell death through SPOP-mediated degradation of ELK3, whereas SPOP deletion or mutation confers docetaxel resistance in prostate cancer cells. This indicates that SPOP mutations may promote tumor cell resistance by affecting ELK3 stability, suggesting a novel therapeutic pathway for SPOP-positive prostate cancer. Furthermore, studies have indicated that ELK3 promotes tumor stemness and resistance to oxaliplatin (48,98). When chemotherapy drugs stimulate tumor cells, autophagy-related signaling pathways are activated and autophagy levels are elevated; this enables tumor cells to degrade chemotherapeutic agents, enhancing their resistance to chemotherapy (99). Park *et al* (100) elucidated the potential mechanism by which ELK3 promotes resistance: Inhibiting ELK3 expression was shown to disrupt autophagy mediated by the PI3K/Akt/mTOR pathway, thereby restoring sensitivity to doxorubicin chemotherapy in breast cancer cells. Another study revealed that ELK3 determines chemotherapy sensitivity to cisplatin in triple-negative breast cancer cells by regulating mitochondrial dynamics. Therefore, inhibiting ELK3 expression holds promise as a potential therapeutic strategy to overcome chemotherapy resistance or induce sensitivity in triple-negative breast cancer (10). Wang *et al* (101) discovered that ELK3 transcriptionally upregulates SERPINE1, which inhibits the ubiquitination of PCBP2, which restricts ferroptosis and consequently induces gefitinib resistance in lung cancer. In ovarian cancer, ELK3 has been verified to function as a transcriptional repressor; it downregulates tropomyosin-2 protein expression to activate

YAP1 signaling, thereby resulting in cisplatin resistance (102). Furthermore, experiments by Peng *et al* (103) confirmed that ELK3 suppresses CHD4 expression and mediates the cisplatin-resistant phenotype. Collectively, available evidence indicates that ELK3 drives tumor chemoresistance through three key mechanisms: Promoting cancer stemness, triggering autophagy and modulating mitochondrial dynamics.

6. ELK3-targeting drugs

As for potent ELK3-targeted small-molecule therapeutics, Wasylyk *et al* (104) identified a novel pyrazole compound, XRP44X, through screening for small-molecule inhibitors targeting Ras-activated ELK3 transcriptional activity in cell-based assays. XRP44X markedly suppresses tubulin polymerization by interacting with the colchicine-binding site. XRP44X consists of four rings (Rings A-D), along with a carbonyl linkage between Rings B and C. Notably, XRP44X is a multifunctional molecule that not only interacts with tubulin but also exhibits diverse biological activities. This compound inhibits ELK3 activation by targeting the Ras-Erk signaling pathway upstream of Ras. Subsequent experiments have demonstrated that XRP44X can suppress tumor growth and reduce metastasis in three distinct mouse models (subcutaneous xenografts, intra-cardiac injection-bone metastasis and TRAMP transgenic mouse model of prostate cancer progression) of tumor progression and metastasis, although minor side effects were observed (105). Kim and Park (106) discovered that XRP44X stimulates NK cells to potentiate their cytotoxicity against breast cancer cells, and while XRP44X exerts no influence on NK cell apoptosis or cell cycle progression, it upregulates interferon-γ production and activates the c-JNK signaling pathway, thereby amplifying NK cell-mediated cytotoxicity. Chen *et al* (107) further demonstrated that XRP44X triggers early activation of the JNK pathway, which induces tubulin depolymerization and G_2/M phase arrest in tumor cells.

7. Conclusion

ELK3 is a key member of the ETS transcription factor family, participating in multiple molecular regulatory pathways and serving roles in various biological processes. The present review provides an initial overview of the structure and function of the ELK3 protein and its impact on biological functions, such as tumorigenesis and progression. Due to alternative splicing of the ELK3 gene, four structurally distinct ELK3 protein isoforms are generated. Nevertheless, existing studies have not yet characterized the biological functions of these isoforms. Regarding full-length ELK3, most research confirms that it binds to ETS consensus motifs within the promoters of target genes to regulate transcription; however, there remains controversy over whether it exerts transcriptional activation or repression. This dual functional discrepancy arises as a dynamic outcome shaped by multiple factors, including the activation status of upstream kinases, the abundance of intracellular co-regulatory molecules, cis-regulatory chromatin elements at target loci, the subcellular localization of the ELK3 protein, crosstalk among multiple signaling cascades, as well as tumor differentiation and pathological stage (108).

Accumulating studies have verified that ELK3 is highly expressed in tumor tissues, and its upregulation is associated with poor clinical prognosis. These findings highlight ELK3 as a central oncogene across multiple solid malignancies. ELK3 acts as an oncogene in tumors, promoting tumor cell proliferation and metastasis, inducing tissue angiogenesis and TME formation, and resulting in chemotherapy resistance. In tumor cells, ELK3 mediates the aforementioned biological functions by acting as a molecular bridge to modulate target gene expression and activate diverse signaling pathways. ELK3 drives cell proliferation through regulating cell cycle progression and c-fos transcription, upregulating oncogenic miRNAs while downregulating tumor-suppressive miRNAs. Accumulating reports have demonstrated that ELK3 regulates its transcriptional activity and isoform expression via RSK2-mediated phosphorylation, thereby affecting the expression of genes related to extracellular matrix degradation such as MMPs, and directly or indirectly governs EMT-related factors and cascades including TGF-β, Wnt/β-catenin and HIF-1α signaling to facilitate tumor metastasis (97). ELK3 indirectly and profoundly affects angiopoietin-mediated vascular remodeling by regulating the HIF-1α/VEGF-A signaling axis, maintaining endothelial barrier stability, and responding to inflammatory signals (80). Studies focusing on ELK3-mediated chemoresistance are relatively comprehensive. ELK3 confers drug resistance via multiple mechanisms: Activating PI3K/Akt/mTOR-dependent autophagy, maintaining cancer stem cell properties, rewiring mitochondrial dynamics, suppressing ferroptosis and modulating YAP1 signaling activity. To date, research exploring the roles of ELK3 in remodeling the tumor immune microenvironment remains limited. Available evidence has suggested that ELK3 promotes the infiltration of M2-type macrophages and suppresses NK cell-mediated tumor cytotoxicity by suppressing CXCL16 expression. Collectively, the specific molecular mechanisms by which ELK3 promotes tumorigenesis and progression remain incompletely elucidated. However, a small number of studies suggest that ELK3 can inhibit tumor progression, potentially due to specific activation mechanisms that alter research conditions (such as when the RSK2 signaling pathway is blocked) and thereby modify ELK3 function. Furthermore, cancer cells often harbor multiple concurrently abnormal intracellular signaling pathways. Future research is therefore needed to explore whether ELK3 possesses broadly targetable common mechanisms.

Given the pivotal role of ELK3 in the progression of multiple types of cancer, ELK3 represents a promising therapeutic target and therapeutic strategies targeting ELK3 are currently under investigation. Specific small-molecule compounds can be screened and candidate drugs rationally designed based on the structural characteristics and regulatory mechanisms of ELK3. Focusing on ELK3 regulatory networks, the present review systematically summarizes upstream transcription factors governing ELK3 expression, critical enzymes mediating ELK3 post-translational modifications, ELK3-targeted miRNAs, as well as ceRNAs that modulate ELK3 activity. Wasylyk *et al* (104) developed XRP44X according to the molecular cascade whereby Ras signaling activates ELK3, and multiple subsequent studies have validated its specific inhibitory effect on ELK3 as

well as its potent antitumor efficacy. With the advancement of personalized precision medicine, improving the understanding of the oncogenic molecular mechanisms of ELK3 and developing ELK3-targeted drugs holds promise for the treatment of malignant tumors. Research on ELK3-targeting anticancer drugs remains limited, with XRP44X representing an early example. Future efforts should focus on screening and optimizing more effective small-molecule inhibitors for the ELK3 target. Additionally, combination therapeutic strategies, integrating ELK3 inhibitors with existing chemotherapeutic agents or immune checkpoint inhibitors, should be considered to overcome drug resistance and enhance therapeutic efficacy. The role and mechanisms of ELK3 in tumor cells discussed in the present review represent only one of numerous factors regulating tumor cell behavior. Ongoing advancements in single-cell technologies, protein structural studies and artificial intelligence, coupled with the initiation of clinical trials for ELK3-targeted drugs, may propel rapid progress in this research field.

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Authors' contributions

ZZL wrote the manuscript as the first author. ZW performed acquisition, analysis and interpretation of data.. ZSL reviewed and revised the manuscript. LQZ guided and supervised the review, reviewed the manuscript and provided funding support. Data authentication is not applicable. All authors have read and approved the final manuscript.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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