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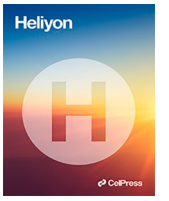

Review article

Mechanisms of tropomyosin 3 in the development of malignant tumors

Anjie Chen [a,b,1], Sixin Li [a,b,1], Jiandong Gui [a,b,1], Hangsheng Zhou [a,b,1], Lijie Zhu [a,**], Yuanyuan Mi [a,*]

[a] Department of Urology, Affiliated Hospital of Jiangnan University, 1000 Hefeng Road, Wuxi, 214122, Jiangsu Province, China
[b] Wuxi School of Medicine, Jiangnan University, 1800 Lihudadao, Wuxi, 214122, Jiangsu Province, China

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ABSTRACT

Tropomyosin (TPM) is an important regulatory protein that binds to actin in fine myofilaments, playing a crucial role in the regulation of muscle contraction. TPM3, as one of four tropomyosin genes, is notably prevalent in eukaryotic cells. Traditionally, abnormal gene expression of TPM3 has been exclusively associated with myopathy. However, recent years have witnessed a surge in studies highlighting the close correlation between abnormal expression of TPM3 and the onset, progression, metastasis, and prognosis of various malignant tumors. In light of this, investigating the mechanisms underlying the pathogenetic role of TPM3 holds significant promise for early diagnosis and more effective treatment strategies. This article aims to provide an insightful review of the structural characteristics of TPM3 and its intricate role in the occurrence and development of malignant tumors.

1. Introduction

Advances in early screening, diagnostic methods, and therapeutic techniques for malignant tumors, particularly with the use of targeted drugs based on second-generation sequencing, have significantly improved the prognosis of some patients with malignant tumors. Despite these strides, malignant tumors remain one of the leading causes of global mortality. The intricate processes of proliferation, invasion, and metastasis in malignant tumor cells pose considerable challenges in the management of patients. Understanding invasive patterns and molecular mechanisms associated with proliferation is essential for effectively treating malignant tumors. Additionally, the exploration and identification of potential biomarkers as specific molecular targets for tumor diagnosis, treatment, and prognosis can enhance patient outcomes by increasing their chances of survival.

Moreover, while high expression of TPM3 in muscle tissues has been extensively linked to the development of fibromyalgia [1], its function in non-muscle cells and tissues remains unclear. Studies suggest that aberrant expression of TPM3 lead to alterations in non-muscle cell environments resulting in changes like neurons morphogenesis, intracellular stress fiber polymerization, E-cadherin and so on [2–5]. For example, in neurons, the low expression level of the Tpm3.1 isoform, affects the morphology of neurons, such as axon length, growth cone size, and dendritic branching [6,7], Tpm3.1, along with other TPM isoforms, play specific roles in the

* Corresponding author.
** Corresponding author.
E-mail addresses: jndxfyzlj@163.com (L. Zhu), miniao1984@163.com (Y. Mi).
[1] These authors contributed equally: Anjie Chen, Sixin Li, Jiandong Gui, Hangsheng Zhou.

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assembly of the cytoskeleton, having different distribution patterns and functions in the formation and maintenance of stress fibers. Furthermore, studies have shown that Tpm3.1 plays an important role in maintaining the stability of intercellular connections in epithelial cells, and its absence leads to a significant decrease in the level of E-cadherin in the kidney [8]. This reduction is closely associated with the occurrence of malignant tumors, including prostate cancer, breast cancer, and gastric cancer, with a predominant decrease in the expression of TPM3 observed in these cancers [9–11].

We provided the review, endeavouring to explore the structure of TPM3, its potential to be biomarker and its role in occurrence, progression, metastasis, and prognosis of malignant tumors. We are entirely convinced that in-depth explorations enable to acheieve new breakthroughs for early diagnosis and more effective treatment strategies in TPM3-related cancers.

2. Structural characteristics of TPM3

All member of TPM family, protein dimers with α-helical coiled-coil structures, are expressed in smooth muscle, skeletal muscle, myocardium, and non-muscle cells [12–14]. It is categorized into two main groups based on molecular weight: the HMW group (248–291 amino acid residues) and the low molecular weight (LMW) group (245–251 amino acid residues [15]) (Table 1). TPM3, belonging to the HMW group along with TPM1 and TPM2, is located in the sub-band 1, band 3, region 2, and long arm of chromosome 1 (1q21.3). It consists of 14 exons, spanning approximately 39 kb of genomic DNA [1,16,17].

The cytoskeletal isomer of TPM3, consisting of 247–248 amino acids (28–30 kDa), includes ten isotypes:Tpm3.12, Tpm3.13, Tpm3.1, Tpm3.2, Tpm3.4, Tpm3.5, Tpm3.7, Tpm3.8 and Tpm3.9. These isoforms differ from each other in amino acid sequence and expression pattern and are involved in the regulation of physiological processes such as cytoskeleton and muscle contraction [15,18]. The HMW group of TPM3, with 285 amino acids (34 kDa), strongly express in skeletal muscle but scarcely in liver, brain, and lung. Mutations in TPM3 lead to autosomal dominant nemaline myopathy and other myopathies, with associated translocations at other loci, such as anaplastic lymphoma kinase (ALK) and neurotrophic tyrosine kinase receptor type 1 (NTRK1), resulting in the formation of fusion proteins acting as oncogenes [19,20]. The gene has multiple pseudogenes on different chromosomes, and selective splicing generates multiple transcript variants, with the human TPM3 gene capable of producing 27 transcripts [21] (Fig. 1).

3. Molecular functions of TPM3 in muscle cells

The protein encoded by the TPM3 gene plays a crucial role in stabilizing actin filaments, regulating the binding of actin with other proteins, and contributing to muscle contraction and cell movement in muscle cells. It particularly regulates actin-myosin ATPase activity and interacts with troponin to form a calcium-sensitive barrier that stabilizes microfilaments, the skeletal structure of myocytes, thus facilitating the regulation of muscle contraction [18,22,23].

Aberrant expression of TPM3 isoforms is associated with various myopathies, ranging from mild to severe presentations. The clinical spectrum of TPM3-related myopathy includes impaired ambulation, feeding difficulties, spine and chest deformities, myopathic facies, facial weakness, foot drop, reduced reflexes, poor muscle bulk, and normal serum creatine kinase levels. Additionally, mild contractures, joint hypermobility, and muscle stiffness may be observed. Notably, extraocular muscles and cardiac function are often spared in TPM3-related myopathy [24].

4. Molecular functions of TPM3 in non-muscle tissues

In non-muscle tissues, actin microfilaments play a pivotal role in diverse cellular functions, including tissue differentiation, intracellular vesicle trafficking, and cell adhesion. The ZA (zonula adherens) constitutes a specialized junction in epithelial cells where E-cadherin and actomyosin bundles converge. Specific isoforms of TPM3 (Tpm3.1, Tpm3.2) have been identified as integral components of the epithelial ZA-linked cytoskeleton [8,25–28]. As an isoform of the TPM family, TPM3 contributes to actin filament stability by modulating actin-myosin interactions, inhibiting the Arp2/3 complex's nucleation at nascent branching sites on actin filaments. TPM3 also regulates other actin-binding proteins, shielding actin filaments from gelsolin-induced cleavage and ADF/cofilin-mediated depolymerization [29,30]. The overexpression of TPM3 has been implicated in stimulating retrograde

Table 1
Genetic information for ten isotypes of TPM3.

Isotypes[a]	Common names	Protein Name[a]	Exon usage
Tpm3.12	Tm ska-slow	Tpm3.12th (a.b.b.a)	1a.2b.3.4.5.6b.7.8.9a
Tpm3.13	–	Tpm3.13cy (a.b.a.d)	1a.2b.3.4.5.6a.7.8.9d
Tpm3.1	Tm5NM1	Tpm3.1cy(b.-.a.d)	1b. _ 0.3.4.5.6a.7.8.9d
Tpm3.2	Tm5NM2	Tpm3.2cy(b.-.b.d)	1b. _ 0.3.4.5.6b.7.8.9d
Tpm3.3	Tm5NM3	Tpm3.3cy(b.-.b.a)	1b. _ 0.3.4.5.6b.7.8.9a
Tpm3.4	Tm5NM4	Tpm3.4cy (b.-.b.c)	1b. _ 0.3.4.5.6b.7.8.9c
Tpm3.5	Tm5NM5	Tpm3.5cy(b.-.a.a)	1b. _ 0.3.4.5.6a.7.8.9a
Tpm3.7	Tm5NM7	Tpm3.7cy (b.-.a.c)	1b. _ 0.3.4.5.6a.7.8.9c
Tpm3.8	Tm5NM8	Tpm3.8cy (b.-.a.a/c)c	1b. _ 0.3.4.5.6a.7.8.9a/c
Tpm3.9	Tm5NM9	Tpm3.9cy (b.-.b.a/c)c	1b. _ 0.3.4.5.6b.7.8.9a/c

[a] The nomenclature follows the recommendation provided by Geeves et al., 2015, *J Muscle Res Cell Motil*

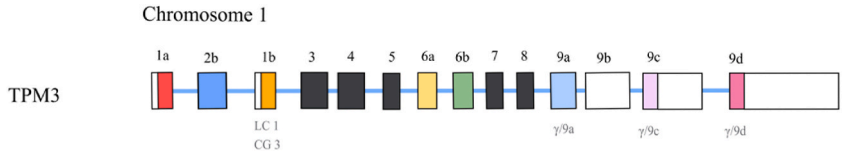

Fig. 1. Schematic representation of the human TPM3 gene (located in chromosome 1). Colored boxes represented coding exons 1 through 9, white boxes represented untranslated 5′ and 3′ UTR sequences, black boxes are exons common to all the genes which share a high degree of homology and lines represented introns.The names of the different tm antibodies (in gray) are located below the corresponding exons.

translocation and the accumulation of membrane-bound organelles in the perinuclear region. This suggests a potential role for TPM3 in organelle distribution, and its involvement in induced organelle movement is associated with microtubules and actin filaments, underscoring TPM3's role in organelle translocation [31]. Recent studies have highlighted the rapid dynamics of short isoforms of TPM3 (Tpm3.1 and Tpm3.2) on actin filaments, showcasing their ability to stimulate the ATPase activity of non-muscle myosin IIa. These findings emphasize how protomyosin isoforms specify the functional properties of distinct actin filament populations [32]. Moreover, TPM3 has been recognized for its crucial role in maintaining cortical actin integrity during oocyte maturation. The dynamic regulation of actin by TPM3 is essential for ensuring asymmetric division, polar body protrusion, and cytoplasmic division [33].

5. TPM3-related gene fusion

TPM3-ALK (anaplastic lymphoma kinase) is an oncogenic fusion protein resulting from chromosomal translocations in inflammatory myofibroblastic tumors (IMT). IMT is a rare disease which is defined as neoplasm of myofibroblastic spindle cells. It can manifest in various organs [34]. The predominant cause of IMT is the fusion gene TPM3-ALK, formed by the fusion of the TPM3 gene with the ALK gene. In 1999, Lamant discovered a novel fusion gene, TPM3-ALK, in anaplastic large cell lymphoma. This brand new gene is due to a chromosome (1; 2) (q25; p23) translocation. They proposed that the TPM3 gene acts as an active promoter for ALK expression. The activation of the ALK catalytic structural domain may be attributed to the dimerization of the heterodimeric protein TPM3-ALK through the protein-protein interaction structural domain of TPM3 [35]. This mechanism has been subsequently confirmed in IMT [36–39], ALK-rearranged renal cell carcinoma [40,41], ALK-positive anaplastic large cell lymphoma [42], and ALK + histiocytosis [42]. Furthermore, TPM3 is implicated in the TPM3-NTRK1 rearrangement and the TPM3-ROS1 rearrangement. TPM3-NTRK1 rearrangement occurs in various types of tumors, such as NTRK-fusion sarcoma of the uterine cervix [43], primary NTRK-rearranged spindle cell neoplasm of the lung [44], invasive mucinous adenocarcinoma of the lung [45], colonic adenocarcinomas with NTRK fusion genes [46]. As for ROS1, an enzyme encoded by the ROS1 gene with receptor tyrosine kinase activity, it is a key regulator of normal cellular activity [47]. TPM3-ROS1 fusions, predominantly observed in non-small cell lung cancer (NSCLC), have been identified with at least 14 ROS1 fusion partner genes, with CD74-ROS1 being the most common. TPM3-ROS1 fusions represent a small proportion (2–3%) of all occurrences of fusion partner genes in NSCLC [48].

6. TPM3 and malignant tumors

Initially, we utilized the GEPIA database to investigate correlations between the TPM3 gene and various malignant tumors. Our analysis revealed varying expression levels of TPM3 across different tumors, with significant differences observed in 15 tumor types compared to normal tissues (Figs. 2 and 4 (A-O)). The GEPIA database further indicated that high expression of TPM3 is associated with enhanced migration and invasion in various cancers. This differential expression of TPM3 at high and low levels in five specific tumors significantly impacts patient prognosis (Fig. 5 (A-E)). Moreover, studies suggest that reduced TPM3 levels may be intricately

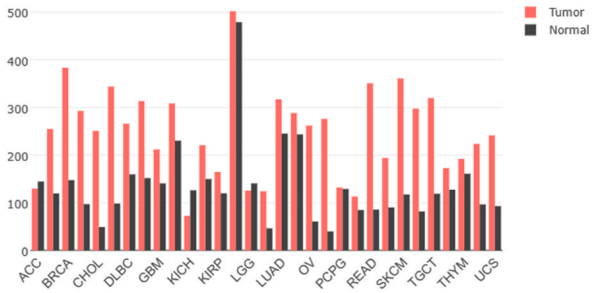

Fig. 2. The TPM3 expression profile across all tumor samples and paired normal tissues from the GEPIA database. Adrenocortical carcinoma (ACC), Breast invasive carcinoma (BRCA), Cholangio carcinoma (CHOL), Lymphoid Neoplasm Difuse Large B-cell Lymphoma (DLBC), Glioblastoma multiforme (GBM), Kidney Chromophobe (KICH), Kidney renal papillary cell carcinoma (KIRP), Brain Lower Grade Glioma (LGG), Lung adenocarcinoma (LUAD), Ovarian serous cystadenocarcinoma (OV), Pheochromocytoma and Paraganglioma (PCPG), Rectum adenocarcinoma (READ), Skin Cutaneous Melanoma (SKCM), Testicular Germ Cell Tumors (TGCT), Thymoma (THYM), Uterine Carcinosarcoma (UCS).

linked to the development of human prostate [10], breast [9,49] and brain tumors [50]. As a member of the TPM family, TPM3 exhibits aberrant expression in multiple cancer types and is closely associated with their progression, including esophageal cancer (EC), renal cell carcinoma, and hepatocellular carcinoma (HCC). TPM3 is also implicated in the regulation of tumor-related genes and signals, such as Matrix metalloproteinases (MMPs) [51], and WEE2-AS1, which may modulate tumor progression by influencing TPM3 and altering cellular motility.

7. TPM3 and EC

In the context of EC, research by Chen et al. has highlighted the role of TPM3 in promoting the proliferation, migration, and metastatic potential of EC cells both in vitro and in vivo. They pointed out that the expression of TPM3 was negatively correlated with tumor stage and prognosis. The higher the expression of TPM3, the lower the 5-year survival rate. The malignant behavior of EC cells induced by TPM3 overexpression can be restored by supplementation of MMP2/9, indicating that TPM3 plays a tumor promotion role by regulating the expression of MMP2/9 to promote EMT process. In conclusion, TPM3 may become a new target for EC treatment and be applied as a prognostic indicator in the clinical management of EC patients [51].

Additionally, Kang et al. identified miR-107 as an inhibitory regulator of TPM3 transcription, inhibiting the proliferation, invasion and metastasis of EC cells. This discovery positions miR-107 as a potential antitumor bioeffector and introduces a novel pathway for targeted therapy in EC [52].

Furthermore, Yu et al. investigated protein expression profiles in esophageal squamous cell carcinoma (ESCC) tissues at different pathological stages. They identified that TPM3 overexpressed in ESCC tissues at stage III compared with stage I. This overexpression of TPM3 may play a role in the invasion and metastasis of ESCC, emphasizing the importance of studying molecular biomarkers associated with ESCC invasion and metastasis for improved clinical screening, diagnosis, and prognosis [53].

8. TPM3 and renal cell carcinoma

Thorner et al. reported a unique case of renal cell carcinoma (RCC) expressing TFE3 without involving a translocation of the TFE3 gene. Usually, translocation-associated RCC is a distinct subtype with gene rearrangements of the TFE3 or TFEB loci, typically resulting in high nuclear expression of TFE3 protein. However, in this case, a translocation between the ALK and TPM3 genes was identified only, instead of the translocation of the TFE3, leading to overexpression of the ALK protein. The patient, initially untreated with chemotherapy, later received ALK inhibitors upon regional lymph node recurrence. The case underscores the importance of detecting TFE3-positive RCC cases lacking ALK expression and translocation, as this subtype may benefit from ALK inhibitor therapy. However, the study did not provide information on the prognosis after treatment [54].

Cajaiba et al. conducted an analysis of 168 pediatric RCC cases, identifying six (3.5 %) cases with unique features, including TPM3-ALK fusion transcripts in three of them. The authors suggested that patients with ALK-rearranged RCC have additional therapeutic options, although the study did not delve into prognosis details [41].

Yu et al. employed immunostaining, fluorescence in-situ hybridization (FISH), and quantitative reverse transcription polymerase chain reaction (RT-PCR) to identify ALK rearrangements in RCC samples. ALK expression was found in two out of 477 RCCs, with further analysis revealing TPM3-ALK and EML4-ALK fusion transcripts in these tumors. Follow-up analysis indicated lower 5-year cancer-specific survival rates for patients with ALK-rearranged RCC compared to certain other RCC subtypes, although higher than that of patients with high-grade RCC. ALK-rearranged RCC was associated with distinct histological features and poor prognosis [55]. Sugawara et al. used an interpolated antibody-enhanced polymer approach to screen 355 tumor tissues and identified two patients with ALK-positive RCC, both having TPM3-ALK and EML4-ALK fusions. The study emphasized the importance of accurate screening methods for detecting ALK fusions and the sensitivity of the interpolated antibody-enhanced polymer immunohistochemical method for detecting EML4-ALK [56]. Additionally, it was noted that the co-helical structure of the TPM3-ALK fusion protein might induce homodimerization of TPM3 and autophosphorylation of the ALK catalytic domain. The transferability of TPM3-ALK fusion protein was suggested to be higher than that of other ALK fusion proteins, and it may be associated with the recombination of other genes, such as VCL and HOOK1 [57]. A rare subtype of adult RCC was described as having an ALK-TPM3 rearrangement in a case report. The patient, a 58-year-old man, presented with a well-characterized renal tumor, confirmed to have ALK gene rearrangement by FISH. This rare subtype poses diagnostic challenges due to its broad histological spectrum. Further studies are warranted to determine the prognostic value of ALK-TRCC [58]. Details of patient cases related to TPM3-ALK fusion are provided in Table 2. The existing evidence suggests that TPM3 may be involved in the occurrence and development of renal cell carcinoma, and TPM3-NTRK1 gene rearrangement is a low-frequency event, with TRKA kinase inhibitors potentially becoming a promising therapeutic approach. However, the specific

Table 2
TPM3-ALK fusion related cases.

References	Age	Gender	Karyotype/CGH	pTNM	Therapy	Follow-up
Thorner et al. [54]	12	Female	t(1; 2)(q21; p23)/ND	–	ALK inhibitor	Alive (1 year)
Cajaiba et al. [41]	14	Male	–	T1aN1M0	–	–
Cajaiba et al. [41]	16	Female	–	T3aN1M0	–	–
Yu et al. [55]	49	Male	–	T1bN1M0	–	Alive (2 years)
Sugawara et al. [56]	36	Female	–	T1aNxM0	–	Alive (2 years)

mechanism of action of TPM3 in renal cell carcinoma still requires further research.

9. TPM3 and HCC

Ching et al. found an elevated expression level of TPM3 in HCC, significantly associated with the expression level of granulin-epithelin precursor (GEP). TPM3 was identified as an interaction partner of GEP, and its high expression was linked to a lower recurrence survival rate in HCC patients. The protein expression of TPM3 and GEP was exclusively observed in the cytoplasm of HCC cells, suggesting an essential role for TPM3 in HCC development [59]. Furthermore, a potential association between TPM3 over-expression and EMT was investigated by Choi et al. Silencing the TPM3 gene significantly inhibited the migration and invasion of HCC cells [60]. TPM3 silencing also hindered colony formation and unanchored growth of HCC cells. Additional analysis revealed that TPM3 overexpression might inhibit the expression of E-cadherin by activating the Snail-mediated EMT pathway, thereby promoting HCC cell migration and invasion. This study marked the first demonstration of TPM3's involvement in HCC migration and invasion, shedding light on its role in modifying the EMT pathway, providing new insights into the mechanism of HCC development, and offering a basis for finding therapeutic targets. Tian et al. explored the relationship between TPM3 up-regulation and HCC, finding that the overexpression of up-regulated TPM3 promotes HCC, consistent with its pro-tumorigenic effect in previous studies [61].

10. TPM3 and papillary thyroid carcinoma

TPM3-NTRK1 rearrangement is one of the mechanisms leading to the occurrence of papillary thyroid carcinoma (PTC). Specifically, the tyrosine kinase domain of the NTRK1 gene fuses with the 5′ end sequence of the TPM3 gene, forming the Trk-T1 fusion gene, and the protein encoded by this fusion gene is continuously phosphorylated, leading to cellular transformation. Brzezianska et al. studied the frequency of RET and NTRK1 proto-oncogene rearrangements in PTC in the Polish population. Analysis of gene sequences from 33 patients with PTC detected by the RT-PCR technique identified four cases of NTRK oncogenic sequences, containing TPM3 sequences. The study hypothesized that TPM3's involvement in the formation of fusion genes plays a driving role in the development of PTC [62].

In an earlier study, Musholt et al. demonstrated that NTRK1, encoding the high-affinity receptor for nerve growth factor, plays a role in the proliferation of various cell types. The tyrosine kinase activation domain at the carboxyl-terminal end of NTRK1 can be rearranged with a variety of genes, with fusion with the amino-terminal end of TPM3 being the most common one [63].

11. TPM3 and lung cancer

TPM3-ROS1 may lead to the sustained activation of ROS1 kinase, thereby participating in the occurrence and development of lung cancer. The incidence of ROS1 fusion genes is relatively low, but due to the high incidence of lung cancer, ROS1 fusion-positive patients still account for a certain proportion. Cao et al. conducted a study detecting ROS1 rearrangements in three patients with lung adenocarcinoma using immunohistochemistry, FISH, and RT-PCR, revealing a prevalence of 1.64 %. Notably, one patient presented with TPM3-ROS1 fusion, emphasizing the diversity of ROS1 rearrangements in this context [64]. In a separate case reported by Zhu et al., a 47-year-old Chinese man with non-small cell lung cancer exhibited a unique scenario of dual fusions involving TPM1-ROS and EML4-ALK. Despite the negative result for Ventana ALK in lung tissue, immunohistochemistry confirmed the presence of ROS1 protein. Next-generation sequencing unveiled both EML4-ALK and TPM3-ROS1 fusions in the tumor, introducing a novel fusion mutation with potential implications for treatment strategies [65]. Li et al. employed next-generation sequencing technology to identify 92 ROS1 rearrangements in lung cancer patients, unveiling 24 ROS1 fusion partners, including 14 new partners and 10 previously reported ones. TPM3-ROS1 emerged as one of the four most common fusion partners, underscoring its significance in the landscape of ROS1 rearrangements [66]. The findings from various research teams further support the evidence of TPM3-ROS1 fusion in studies exploring ROS1 fusion genes in lung cancer [67]. Rapid and accurate detection of ROS1 fusion and understanding of its clinicopathological characteristics are vital to the precise treatment of lung cancer.

12. TPM3 and colorectal cancer (CRC)

TPM3-NTRK1 rearrangement is a common event in CRC. In CRC cell line KM12, the TPM3 promoter drives the ectopic expression of the NTRK1 gene, producing the TPM3-TRKA chimeric protein which activates the sustained activity of the TRKA tyrosine kinase, thereby promoting tumor cell growth and transformation.

Detailed analysis of Elena et al. in the TPM3-NTRK1 gene rearrangement uncovered a novel and highly potent TRKA inhibitor named NMS-P626. This inhibitor demonstrated the ability to effectively inhibit the phosphorylation and downstream signaling of TPM3-TRKA in KM12 cells. KM12 cells were highly sensitive to TRKA kinase inhibitors. Furthermore, in a mouse model featuring KM12 tumors harboring the TPM3-NTRK1 gene rearrangement, NMS-P626 exhibited significant antitumor activity, highlighting its potential therapeutic efficacy. The researchers extended their investigation to clinical CRC specimens, employing quantitative reverse transcription PCR and IHC. Through these methods, they successfully detected the presence of TPM3-NTRK1 gene rearrangement in CRCs. This discovery suggests that TPM3-NTRK1 gene rearrangement recurrently occurs in CRCs. The promising results with NMS-P626 indicate that TRKA kinase inhibitors could be a viable treatment option for patients with tumors carrying NTRK1 gene rearrangements. This insight opens new avenues for targeted therapies in **CRC** [68].

Kim et al. observed that CRCs with TPM3-NTRK1 fusions exhibit specific molecular features, including high microsatellite

instability (MSI-high), high CpG island methylation (CIMP-high), MLH1 methylation, and BRAF/KRAS wild type. Unlike other NTRK fusion-positive CRCs, those with TPM3-NTRK1, TPR-NTRK1, LMNA-NTRK1, SFPQ-NTRK1, or EML4-NTRK3 fusions displayed recognizable moderate (2+) or intense (3+) TRK immunohistochemical staining intensity. The TPM3-NTRK1 fusion serves to characterize the molecular features of NTRK fusion-positive CRCs, offering insights into potential therapeutic strategies [69].

13. TPM3 and IMT

IMT is characterized by myofibroblastic spindle cells and frequent plasma cell or lymphocyte infiltration. Key fusion partners identified include TPM3/4, CLTC, and RANBP2 genes [70]. ALK gene rearrangements, particularly the TPM3-ALK fusion gene, are major contributors to IMT. The coiled-coil structure of TPM3 potentially promotes dimerization of the TPM3-ALK fusion protein, leading to autophosphorylation of the ALK catalytic structural domains [35,37]. Studies by Amano et al. [71] using blue native polyacrylamide gel electrophoresis highlighted the dimerization process of TPM3-ALK fusion protein. Giuriato et al. demonstrated the essential role of TPM3-ALK in tumor growth and maintenance, with tyrosine kinase inhibitors showing efficacy in inhibiting tumor growth [72]. Armstrong et al. revealed alterations in cytoskeletal structure and increased cell motility in TPM3-ALK-expressing cells. In subsequent investigations, the researchers employed immunoprecipitation experiments and an experimental lung metastasis model to unravel further insights into the impact of TPM3-ALK fusion protein expression. Their findings revealed that the expression of TPM3-ALK fusion protein induces notable changes in cytoskeletal organization, endowing cells with a heightened metastatic capacity when compared to other ALK fusion proteins [73]. The specific interactions identified between TPM3-ALK and endogenous pro-myosin, coupled with the disruption of stress fibers, were highlighted as potential contributors to the altered cell morphology and increased cell motility observed in TPM3-ALK-expressing cells. These unique properties of TPM3-ALK fusion proteins set them apart and suggest a distinct influence on cell behavior, morphology, and tumorigenesis [20]. The understanding of these properties provides valuable insights into the potential mechanisms underlying the enhanced metastatic capacity associated with TPM3-ALK fusion proteins.

14. TPM3 and melanocytic neoplasms

Spitzoid melanocytic neoplasms, including Spitz nevus (SN), atypical Spitz tumor (AST), and Spitzoid melanoma (SM) [74,75], exhibit a spectrum of melanocytic lesions. Saraggi et al. conducted an extensive investigation into the prevalence of ALK gene alterations within a substantial series of Spitzoid lesions, SN, AST, and SM. Through ALK immunohistochemistry and FISH analysis of 78 Spitzoid clustered lesions, they identified ALK gene rearrangements in 14.6 % of SN and 13.8 % of AST, while SM exhibited ALK negativity. Notably, the fusion partner genes TPM3 and DCTN1 were identified in two of the translocated cases. The significance of TPM3-ALK fusions within melanocytic neoplasms was emphasized by Klaus, who utilized FISH to confirm ALK rearrangements in all cases. Quantitative polymerase chain reaction identified TPM3 as the fusion partner in 11 cases, alongside 6 cases involving dynactin 1 [76]. Catherine et al. further underscored TPM3's role as a gene cooperating with ALK in gene fusion in Spitz tumors. They highlighted TPM3 as an adapter protein connecting melanosomes to tropomyosin and actin. The myovar-melanophilin complex demonstrated a preferential binding to actin-TPM3.1, facilitating efficient metastasis [77]. In a study characterizing ROS1 fusion Spitz tumors, Gerami et al. analyzed clinical, morphological, and genomic features of 17 ROS1 fusion Spitz tumors, comparing them with a cohort of 99 non-ROS1 Spitz tumors. The characteristic microscopic features of ROS1 fusion tumors included a plaque-like or nodular silhouette, densely cellular intraepidermal melanocyte proliferation, pagetosis, and spindle cell cytomorphology. The study also identified different binding partners to ROS1, with PWWP2A and TPM3 being the most common [78]. These findings contribute to a deeper understanding of the molecular landscape and characteristics of Spitzoid lesions with ALK and ROS1 alterations.

15. TPM3 and glioma

Glioma is a prevalent central nervous system tumor accounting for approximately 81 % of malignant brain tumors [79], characterized by a high mortality and morbidity rate [80]. Huang et al. conducted a study exploring the association between TPM3 expression and patient survival in patients with glioma. Through survival analysis and Cox regression analysis, they found that high TPM3 expression in all age groups was correlated with poorer prognosis. Specifically, among histologic types of gliomas, elevated TPM3 expression was significantly linked to a worse prognosis in astrocytomas and oligodendrogliomas. This suggests that TPM3 overexpression enhances glioma proliferation and tumorigenicity, establishing TPM3 as an independent prognostic factor for glioma [81]. In the context of glioma development, aberrant expression of the long non-coding RNA SNHG9 has been reported to promote glioma progression through the miR-326/SOX9 axis [82,83]. Building on this, Jia et al. explored the regulatory network involving WEE2-AS1, miR-29b-2-5p, and TPM3. They demonstrated that WEE2-AS1 regulates TPM3 expression by interacting with miR-29b-2-5p. Down-regulation of WEE2-AS1 led to indirect regulation of TPM3, resulting in the inhibition of proliferation, migration, and invasion abilities in glioma cells [84].

16. TPM3 and cervical cancers

Zhao et al. highlighted the crucial role of TPM3 in cervical cancer and its association with various malignant tumors. Leveraging RNA sequencing data from the Cancer Genome Atlas, they evaluated TPM3 expression and its relationship with cervical cancer prognosis. The study utilized receiver operating characteristic curves and found that elevated TPM3 mRNA and protein levels in

cervical cancer samples were associated with low overall survival. This confirmed TPM3 as a key regulator in cervical cancer progression, prognosis, and the tumor immune microenvironment. The findings suggested that TPM3 has the potential to serve as a biomarker for the diagnosis and prognosis of cervical cancer [85]. Researches from Wang et al. drew similar conclusions. They found that in cervical cancer tissues, the expression of TPM3 is significantly upregulated, and its high expression is associated with poor prognosis of patients, which suggests that TPM3 may serve as an important biomarker for cervical cancer [86]. Tsai et al. indicated that the cervix was the most common site of occurrence for adult NTRK-rearranged visceral spindle cell tumors, accounting for 62 % of cases. Among these NTRK-rearranged cervical cancers, the TPM3-NTRK1 fusion gene was the most common, accounting for 54 % of cases. These NTRK-rearranged cervical cancers showed a broad morphologic spectrum, ranging from low to moderate malignancy to highly malignant sarcomas, and sometimes heterogeneous differentiation was seen. In conclusion, the TPM3-NTRK1 fusion gene is a common molecular feature in adult NTRK-rearranged cervical cancers. These cancers exhibit diverse histologic patterns, which pose a diagnostic challenge [87]. Rabban et al.also pointed out that TPM3-NTRK1 gene fusion, as a rare type of cervical cancers, presents as a macroscopically visible mass or polyp in the cervix, histologically showing a high-cellular spindle cell proliferation with residual cervical glands. Studies have shown that these cervical cancer cells express S100 and pan-Trk proteins, which suggests that the diagnosis should take the possibility of an NTRK fusion into account, which can be identified using IHC or molecular tests [88].

17. Discussion

Earlier investigations had indicated that the TPM3 gene, belonging to the TPM family, encodes a rhabdomyosin isoform through a variable splicing mechanism. Its primary role involves encoding proteins in muscle tissue that contribute to stabilizing actin fibers, regulating actin binding to other proteins, and facilitating contractile effects on muscle. Abnormal expression of TPM3 in myopathy has been the subject of extensive research. Among these studies, congenital fiber type disorder emerged as the most common diagnosis, accounting for 51 % of cases. Congenital fiber type disorder is characterized by selective atrophy of type 1 muscle fibers. Additionally, linear myopathy, comprising 29 % of cases, was identified as the second most prevalent diagnosis. Linear myopathy is marked by the presence of linear rods [1]. Patients with these conditions may exhibit symptoms such as muscle weakness and fatty infiltration between muscle fibers in various parts of the circumference. In some cases, individuals may experience generalized muscle weakness. These mechanisms and findings have been discussed in previous studies, shedding light on the diverse manifestations of abnormal TPM3 expression in myopathic conditions [89–91].

The advent of next-generation sequencing has uncovered a plethora of TPM3-associated disorders across various carcinomas, some of which are exceptionally rare case reports. This study underscores the pivotal role of TPM3 in the development and progression of diverse cancers, including HCC, thyroid carcinoma, and CRC. The observed overexpression of TPM3 is consistently linked to increased migration, invasion, and colony formation of cancer cells, indicative of its pro-tumorigenic effects. In HCC, TPM3 overexpression is associated with the activation of the EMT pathway, leading to the inhibition of E-cadherin expression and promoting cell migration and invasion. In EC, miR-107 has been identified as an inhibitory regulator of TPM3, presenting a potential anti-tumor bioeffective molecule and a novel avenue for targeted therapy.

Moreover, the study highlights three prominent TPM3 fusions in various carcinomas. In PTC, TPM3-NTRK1 fusion is detected,

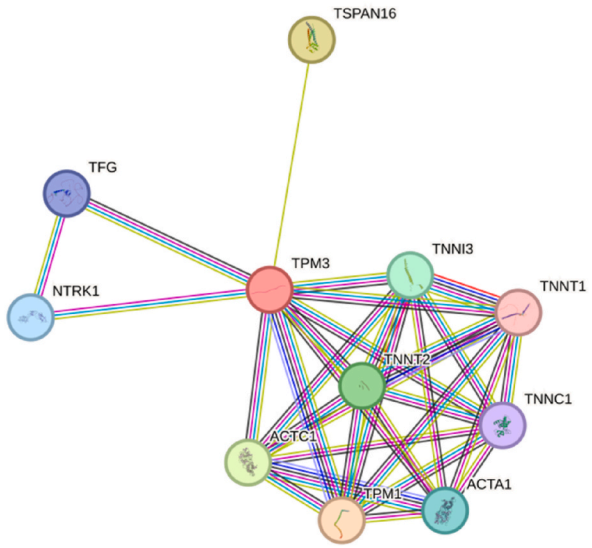

Fig. 3. Protein-protein interaction (PPI) network analysis of 10 interacting proteins correlated with TPM3.
TSPAN16 (tetraspanin 16), TFG (TRK-fused gene), NTRK1 (neurotrophic tyrosine kinase receptor type 1), TNNI3 (troponin I type 3), TNNT1 (troponin t type 1), TNNT2 (troponin t type 1), TNNC1 (troponin c type 1), ACTC1 (actin alpha 1, cardiac muscle), TPM1 (tropomyosin 1), ACTA1 (actin alpha 1,skeleton muscle).

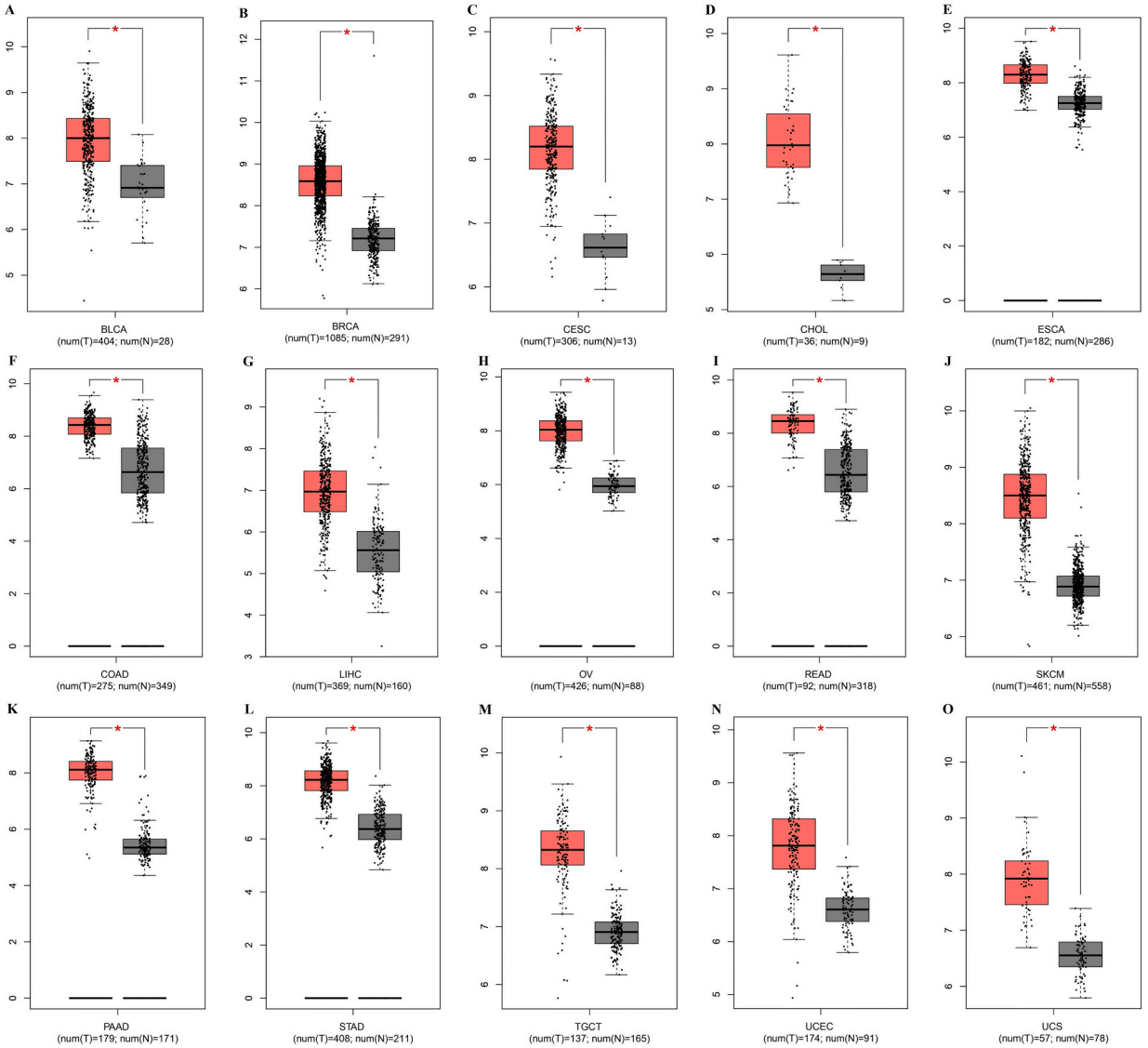

Fig. 4. According to the GEPIA database, it was further found that the data of 15 tumor samples and paired normal tissues had significant differences in TPM3 expression (red rectangles: tumors, black rectangles: paraneoplastic controls). **A.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in BLCA (bladder urothelial carcinoma), number tumor samples = 404, number paired normal tissues = 28 (num(T) = 404; num(N) = 28), $P \leq 0.05$. **B.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in BRCA, num(T) = 1085; num(N) = 291, $P \leq 0.05$. **C.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in CESC (cervical squamous cell carcinoma and endocervical adenocarcinoma), num(T) = 305; num(N) = 13, $P \leq 0.05$. **D.** The TPM3 gene expression of tumor samples were higher than paired normal tissues in CHOL,num(T) = 36; num(N) = 9, $P \leq 0.05$. **E.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in ESCA (esophageal squamous cell carcinoma), num(T) = 182; num(N) = 288, $P \leq 0.05$. **F.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in COAD (colon adenocarcinoma), num(T) = 275; num(N) = 349, $P \leq 0.05$. **G.** The TPM3 gene expression of tumor samples were higher than paired normal tissues in LIHC (liver hepatocellular carcinoma), num(T) = 369; num(N) = 160, $P \leq 0.05$. **H.** The TPM3 gene expression of tumor samples were higher than paired normal tissues in OV, num(T) = 426; num(N) = 88, $P \leq 0.05$. **I.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in READ, num(T) = 92; num(N) = 318, $P \leq 0.05$. **J.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in SKCM, num(T) = 481; num(N) = 558, $P \leq 0.05$. **K.** TPM3 gene expression of tumor samples were higher than paired normal tissues in PAAD (pancreatic adenocarcinoma), num(T) = 179; num(N) = 171, $P \leq 0.05$. **L.** TPM3 gene expression of tumor samples were lower than paired normal tissues in STAD (stomach adenocarcinoma), num(T) = 408; num(N) = 211, $P \leq 0.05$. **M.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in TGCT, num(T) = 137; num(N) = 165, $P \leq 0.05$. **N.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in UCEC (uterine corpus endometrial carcinoma), num(T) = 174; num(N) = 91, $P \leq 0.05$. **O.** The TPM3 gene expression of tumor samples were lower than paired normal tissues in UCS, num(T) = 57; num(N) = 78, $P \leq 0.05$.

hypothesized to play a driving role in PTC development. In lung adenocarcinoma, TPM3 fuses with ALK and ROS1, emphasizing its significance in the pathogenesis of diverse cancers. In CRC, TPM3-NTRK1 gene rearrangement results in the expression of TPM3-TRKA fusion protein with oncogenic potential. In IMT, TPM3-ALK fusion is widespread, and its overexpression and activation are deemed vital causes of IMT.

Understanding the regulatory pathways and mechanisms of TPM3 fusion genes in various malignant tumors holds the key to devising effective treatments and extending life expectancy. Notably, in EC research, miR-107 emerges as a potential anti-tumor bioeffective molecule, offering a new avenue for targeted therapy. In RCC, where TPM3-NTRK1 gene rearrangement is a low-frequency event, TRKA kinase inhibitors may present a promising therapeutic approach for patients with tumors carrying NTRK1 gene rearrangements.

Additionally, to unravel the genes interacting with TPM3 and gain deeper insights into its biological role, we constructed a protein-protein interaction network to identify functional partners of TPM3. The results revealed associations with TSPAN16 (tetraspanin 16), TFG (TRK-fused gene), NTRK1, TNNI3 (troponin I type 3), TNNT1 (troponin t type 1), TNNT2 (troponin t type 1), TNNC1 (troponin c type 1), ACTC1 (actin alpha 1, cardiac muscle), TPM1, ACTA1 (actin alpha 1, skeletal muscle) (Fig. 3).

18. Conclusion

In summary, this study provides a comprehensive overview of the biological functions of TPM3 in both muscle and non-muscle cells, as well as its role in tumorigenesis and development. TPM3's involvement in stabilizing actin filaments, regulating actin binding, and facilitating muscle contraction and cell movement in muscle cells has been well-documented. In non-muscle cells, it plays a role in tissue differentiation, intracellular vesicle trafficking, and cell adhesion by encoding actin microfilaments. Aberrant expression of TPM3, along with its extensive role as a fusion gene chaperone in various malignant tumors, suggests its potential as a tumor biomarker. While studies have shed light on TPM3's involvement in specific malignancies, further research is warranted to explore its role in tumors across other organs and systems. The utilization of the GEPIA database and the String online website has

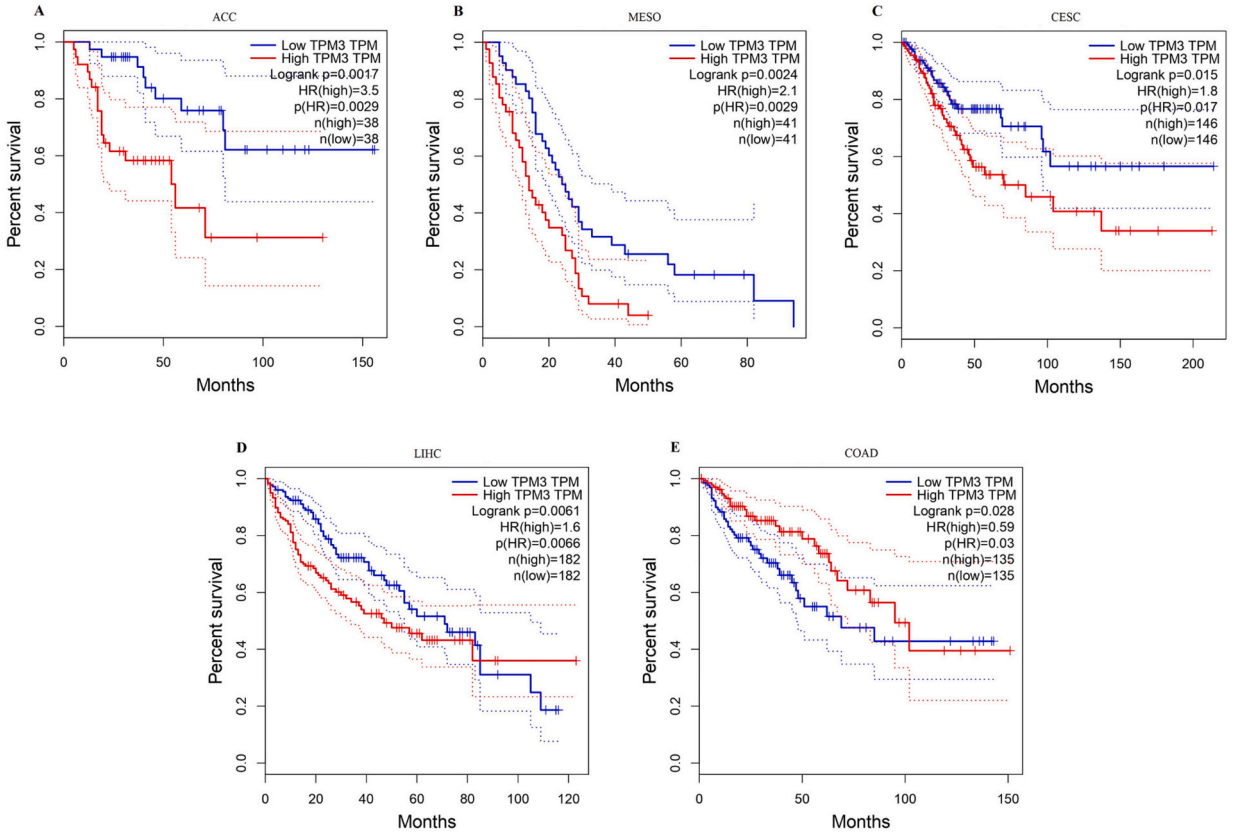

Fig. 5. The effect of different expressions of TPM3 on overall survival in some patients with malignant tumors from GEPIA database (blue lines: low TPM3 TPM, red lines: high TPM3 TPM). Low TPM3 TPM had a better OS than high TPM3 TMP in ACC (adrenocortical carcinoma), n (high) = 38, n (low) = 38, $P \leq 0.05$. **A.** Low TPM3 TPM had a better OS than high TPM3 TMP in MESO (mesothelioma), n (high) = 41, n (low) = 41, $P \leq 0.05$. **B.** Low TPM3 TPM had a better OS than high TPM3 TMP in CESC, n (high) = 146, n (low) = 146, $P \leq 0.05$. **C.** Low TPM3 TPM had a better OS than high TPM3 TMP in LIHC, n (high) = 182, n (low) = 182, $P \leq 0.05$. **D.** High TPM3 had a better OS than low TPM3 TMP in COAD, n (high) = 135, n (low) = 135, $P \leq 0.05$.

provided valuable insights into TPM3-related malignancies and associated proteins. Continued exploration may pave the way for the development of targeted drugs, ultimately contributing to increased life expectancy for patients with TPM3-related malignancies.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this is a review. Informed consent was not required for this study because this is a review.

Data availability statement

Question: Has data associated with your study been deposited into a publicly available repository?
Response: No, data availability is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Anjie Chen: Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Sixin Li:** Writing – review & editing. **Jiandong Gui:** Writing – original draft, Visualization. **Hangsheng Zhou:** Writing – review & editing, Visualization. **Lijie Zhu:** Supervision, Funding acquisition. **Yuanyuan Mi:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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