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Tropomodulin-1—From the actin slow-growing end to multifunctional roles

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Tropomodulin-1 (TMOD1) is a key regulator of actin filament dynamics that functions as an actin-binding protein. It specifically caps the slow-growing (pointed) ends of actin filaments, and the interaction is further stabilized by tropomyosin (TPM). By modulating actin monomer polymerization and depolymerization, TMOD1 critically controls filament length, thereby maintaining both the stability and plasticity of actin-based structures. Emerging evidence has highlighted the participation of TMOD1 in diverse cellular processes, such as cytoskeletal organization, neurite outgrowth, cell motility, and cancer progression. This review summarizes recent advances in TMOD1 research and offers a comprehensive overview of its multifaceted biological roles and implications for future studies.

Keywords: actin; biological functions; cancer; cell morphology; heart; kidney; nervous system; slow-growing end; tropomodulin-1

The tropomodulin (TMOD) family comprises evolutionarily conserved ~40 kDa proteins [1,2]. In vertebrates, four isoforms (TMOD1, TMOD2, TMOD3, and TMOD4) exhibit distinct tissue-specific expression patterns: TMOD1 is highly enriched in terminally differentiated cells, including erythrocytes, lens fibroblasts, neurons, and striated muscle cells [3–5]; TMOD2 is predominantly localized in the nervous system [6]; TMOD3 is ubiquitously distributed across tissues [7]; and TMOD4 is exclusively found in skeletal muscle fibers [8]. Despite their differential expression, all of the isoforms share 70–80% amino acid sequence similarity. A hallmark feature of the TMOD family is their ability to cap the slow-growing (pointed) ends of

Abbreviations
CDK1, cyclin-dependent kinase 1; D-loop, DNase-binding loop; FLII, flightless-I homolog; GLD, gelsolin-like domain; K_d, equilibrium dissociation constant; LRR, leucine-rich repeat; NLRP1, NOD-like receptor protein 1; NLS, nuclear localization signal; TB10, tubercle bacillus 10; TMOD, tropomodulin; TPM, tropomyosin; ZNF407, zinc finger 407.

actin filaments, thereby modulating actin dynamics. Accumulating evidence in the literature underscores their functional roles in diverse biological processes, including neurite outgrowth [6], cell migration [7], and apoptosis [9].

Among these isoforms, TMOD1 is the most extensively characterized. It binds tropomyosin (TPM) and caps the pointed ends of actin filaments, significantly stabilizing actin filaments by inhibiting their depolymerization [10]. In addition to its canonical capping function, TMOD1 interacts with actin monomers, potentially influencing nucleation [11]. Genetic ablation studies have highlighted the essential role of TMOD1 in development: *TMOD1* knockout in mice results in embryonic lethality at embryonic day (E) 9.5–10.5, accompanied by severe defects, such as myofibril disorganization, fragile yolk sac erythroid cells, and impaired vascular remodeling [12].

Structure of TMOD1

The coding sequence of TMOD1 is highly conserved across species, including humans, mice, rats, and chickens. In humans, the *TMOD1* gene is located on chromosome 9q22.1–22.2, and it comprises nine exons, with transcription initiated by a tissue-specific promoter upstream of exon 1 [13].

TMOD1 consists of an unstructured N-terminal domain and a C-terminal domain containing four and a half leucine-rich repeats (LRRs) [14,15]. The LRR domain of TMOD1 is structurally stable and compact [16]. Although the deletion of the LRR domain does not affect TMOD1 actin-capping activity *in vitro*, its absence impairs the localization of TMOD1 at the pointed ends of myofibrils in cardiac muscle cells [17]. Two TPM-binding sites were identified within the N-terminal region of TMOD1: one spanning amino acid residues 1–38, which binds skeletal muscle TPM1.1 isoform; another at residues 109–144, capable of binding both muscle and non-muscle TPM1 isoforms (Fig. 1A) [18,19]. The mutant targeting the first TPM-binding site (TMOD1^{L27G}) and that targeting the second TPM-binding site (TMOD1^{I131D}) both exhibit reduced TPM-binding activity [20]. TMOD1^{L27G} shows severely impaired localization at the pointed ends of thin filaments, whereas TMOD1^{I131D} localizes almost normally. The double mutant TMOD1$^{L27G/I131D}$ nearly abolishes both TPM binding and targeting the pointed ends of thin filaments in cardiomyocytes [20]. Similarly, mutations in the first TPM-binding site (TMOD1$^{R11K/D12N}$) and that in the second TPM-binding site (TMOD1^{Q144K}) have significant effects on the binding affinity of this protein to TPM; meanwhile, the double mutant TMOD1$^{R11K/D12N}$ and triple mutant TMOD1$^{R11K/D12N/Q144K}$ significantly reduce actin filament capping activities (Fig. 1B) [21].

The N-terminal domain and C-terminal domain of TMOD1 each have actin-binding sites located at amino acid residues 50–101 and 160–349, respectively (Fig. 1A) [15]. Mutations such as TMOD1^{L71D} and TMOD1^{R189W} impair the pointed-end capping function of TMOD1 (Fig. 1B) [16,22]. The actin-binding capability of the C-terminal part of TMOD1 protein (residues 160–359; $K_d \approx 0.4$ μm) exhibits stronger actin binding than the N-terminal fragment (residues 1–130; $K_d \approx 1.8$ μm) [23]. Moreover, the pointed-end capping activity of full-length TMOD1 increases approximately four-fold in the presence of TPM ($K_d \approx 28$ nM), compared to in its absence ($K_d \approx 108$ nM) [15]. Meanwhile, it should be noted that measured affinity values may vary across experiments due to differences in the number of available filamentous actin pointed ends [15]. Moreover, the α-helix in the C-terminal domain of TMOD1 protein (residues 160–359) but not in the N-terminal domain (residues 1–130) promotes actin nucleation, which is independent of TPM, which indicates that the C-terminal domain binds to two actin subunits at the pointed end, whereas the N-terminal domain binds to only one actin subunit [11,23]. Additionally, residues 170–179 in the C-terminal domain are critical for interaction with the DNase I-binding loop (D-loop) of actin (Fig. 1A) [24].

TMOD1 and cell morphology

Actin participates in the formation of various structural elements within cells, such as sarcomeres in muscle cells and junctional complexes in the membrane skeleton of non-muscle cells. The stability of the actin structure requires strict regulation of the actin filament length. Loss of *TMOD1* expression sometimes leads to compensatory expression of other TMOD family members [25]. Different combinations of TMOD isoforms in cells help maintain the dynamics and stability of actin, thereby creating cell-specific actin structures that meet the physiological requirements of different cells [5,8,25].

Mammalian erythroid cells possess a hexagonal network-like cytoskeletal structure beneath their membranes, providing unique deformability and extensibility that is crucial for efficient passage through the microvascular system. The erythroid cell membrane skeleton is composed of short actin filaments, TPM, TMOD1, and spectrin [26]. The TMOD1–TPM1.8/TPM1.9 complex acts as a molecular ruler,

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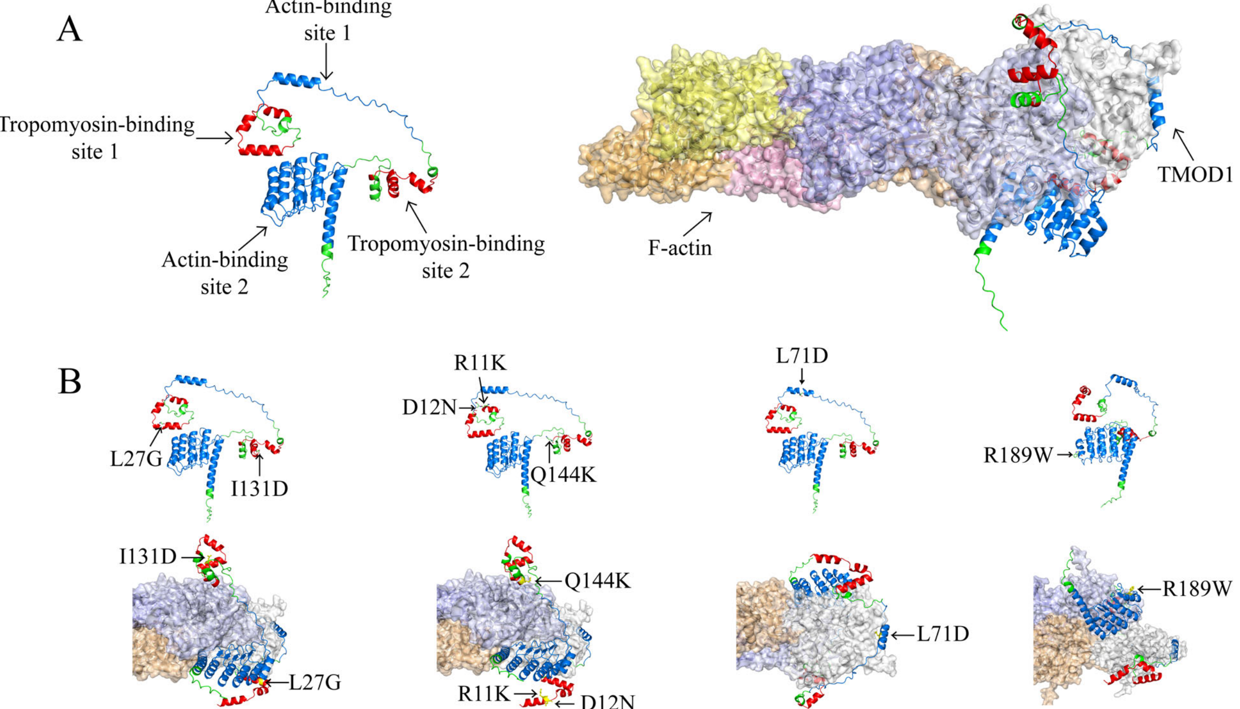

Fig. 1. Protein structure of TMOD1 and its interaction with actin. (A) The predicted structure of the TMOD1 monomer was retrieved from the AlphaFold Protein Structure Database (https://alphafold.com; ID: AF-P28289-F1). The predicted structure of the TMOD1-F-actin complex was generated from the AlphaFold Server (https://alphafoldserver.com). Structural visualization was performed using PyMOL (version 3.1.6.1). In the TMOD1 protein structure, the blue regions represent the actin-binding sites, the red regions denote the tropomyosin-binding sites, and the green regions correspond to the remaining portions of the protein. (B) The predicted structures of TMOD1 mutants and their interactions with F-actin were generated using templates derived from the AlphaFold Protein Structure Database and the AlphaFold Server, respectively. All structures were visualized using PyMOL (version 3.1.6.1).

maintaining an actin filament length of approximately 37 nm [3]. The dysfunction of membrane skeleton proteins can lead to an abnormal erythroid cell shape, reduced deformability, and decreased stability, causing hemolytic anemia in both mice and humans [27].

Past studies with *TMOD1* gene-knockout mice have highlighted the role of TMOD1 in immature and mature erythroid cells. *TMOD1*-deficient mice exhibit mild hemolytic anemia, reduced deformability, and decreased membrane permeability [12]. Another study revealed the compensatory role of TMOD3 in the absence of TMOD1 during erythroid cell maturation [25]. TMOD3 is produced in precursors and recruited to the membrane skeleton, covering the pointed ends of actin filaments when TMOD1 is absent in mature erythroid cells. Insufficient TMOD3 levels or functional changes can disrupt late-stage actin filament assembly, leading to abnormal spectrin–actin networks that resemble spherocytic elliptocytosis in mature erythroid cells [25]. A recent study has indicated the involvement of TMOD1 in the enucleation of human and mouse erythroid cells by regulating actin filaments in the posterior nuclear region [28].

The hexagonal geometric shape of lens fiber cells represents a prototypical model of the epithelial cell hexagonal aggregation observed in various tissues and organs. The maintenance of this hexagonal shape and arrangement of fiber cells depends predominantly on the spectrin–actin cytoskeleton. This cytoskeletal framework primarily consists of α2β2 spectrin chains that link to actin filaments stabilized by TPM, with actin filaments further secured by the N-terminal cap of TMOD1 [4]. Nowak et al. utilized $TMOD1^{-/-Tg(\alpha\text{-}MHC\text{-}TMOD1)}$ mice, which express *TMOD1* only in heart cells, to investigate the impact of *TMOD1* gene knockout on mouse lens morphology and function [4]. Initially, fiber cell morphology in *TMOD1*-deficient mice appeared normal. However, with cell maturation, abnormal membrane protrusions emerge, disrupting the hexagonal structure of the fiber cells. The fiber cells show reduced TPM levels in the cell membrane skeleton, decreased filamentous actin on the

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membrane, disrupted connections between spectrin–actin cytoskeletons, disturbed membrane tension balance, and membrane instability, thus leading to altered cell–cell interactions and disordered fiber cell arrangements [29]. Another study highlighted the critical role of TMOD1 in forming large paddle-shaped domains between mature fiber cell membranes [30].

In skeletal muscle cells, the barbed ends are anchored to the Z-line, whereas the pointed ends are fixed in the middle of the sarcomere [31]. The dynamic properties of actin polymerization and depolymerization within sarcomeres are crucial for their biological functions [32]. TMOD1 regulates actin dynamics to control fiber length and organize the sarcomere arrangement, which is crucial for skeletal muscle contraction [33]. In *TMOD1*-deficient skeletal muscles, TMOD3 and TMOD4 located at the myofilament ends compensate through increased expression to maintain normal skeletal muscle structure, myofiber assembly, and filament length [5]. However, TMOD1 loss still results in reduced isometric tension during muscle contraction, leading to functional defects in the skeletal muscle system. Thus, although TMOD3 and TMOD4 can structurally compensate for the absence of TMOD1, they cannot fully compensate for the functional deficiencies [34], which underscores the indispensable role of TMOD1 in skeletal muscle.

TMOD1 and the heart

TMOD1 is the sole TMOD isoform expressed in cardiomyocytes [35]. In these cells, TMOD1 dynamically interacts with TPM and actin to maintain the mature cardiac muscle fiber length and myofibril structure in the myocardium [36]. During embryonic heart development, TMOD1 participates in processes such as vascular generation in the embryonic yolk sac and heart looping [37]. Embryonic mice lacking TMOD1 exhibit normal development before E7.5; but by E8.5, they show defects in myofibrillogenesis; by E9.5, they exhibit developmental arrest and embryonic lethality ensues [37].

Cardiomyocytes from *TMOD1* gene-deficient mouse embryos exhibit abnormal actin bundles that fail to mature into myofibrils of normal length, thus resulting in significant cardiac defects, such as primitive hematopoietic abnormalities and abnormal vascular morphology [38]. Embryonic mice lacking the TMOD1 protein display intracardiac erythrocyte aggregation, vascular developmental defects in the yolk sac, severe embryonic growth retardation, heart pump failure, and ultimately embryonic death [38]. Moreover, TMOD1 appears to have temporal specificity in myofibril assembly, with involvement in the early cardiomyocyte membrane and late filament length regulation [39]. Overexpression of *TMOD1* in mouse cardiomyocytes shortens filament length, leading to dilated cardiomyopathy, intercalated disc alterations, myofibrillar degeneration, impaired myocardial contractility, and heart failure [39]. Leiomodin-2 (LMOD2) competes with TMOD1 to extend filaments [40], and the interaction of TMOD1 or LMOD2 in the gelsolin-like domain (GLD) region is crucial for the flightless-I homolog (FLII) to influence filament length [41]. Therefore, precise stoichiometry between TMOD1 and other sarcomeric proteins is critical for maintaining normal heart function.

TMOD1 and the nervous system

The expression of *TMOD1* was detected in neurons within the olfactory bulb, hippocampus, cerebral cortex, and basal ganglia of the brain using *in situ* hybridization [42]. Fath et al. observed that *TMOD1* expression increases during neurite extension. In the later stages of neuronal development, TMOD1 concentrates at the proximal ends of actin filament bundles in the lamellipodia of migrating cells and growth cones of neurites [6]. Fath et al. also provided the initial evidence that TMOD1 acts as a negative regulator of neurite growth and crucially influences neurite formation and extension [6]. However, Gray et al. reported that *TMOD1* overexpression promotes dendrite formation and increases dendritic termini and total dendritic length in neurons (Fig. 2A) [43,44]. Overexpression of *TMOD1* increased the number of filopodia and the total number of spines, whereas downregulation of *TMOD1* disrupted spine morphogenesis and impaired synapse formation (Fig. 2B) [42,43]. The TMOD1^{L71D} mutation with disrupted actin filament capping activity failed to promote the formation of thin spines [44]. Recent research has also highlighted that the interactions involving *TMOD1* expression, NOD-like receptor protein 1 (NLRP1), and zinc finger 407 (ZNF407) mutations influence the development of anxiety and depression related to alcohol consumption [45].

TMOD1 and cancer

Increasing evidence suggests that the role of TMOD1 in actin dynamics is related to cancer development. It has been reported that, in ovarian cancer cells, the actin-binding site on the TMOD1 protein also serves as the binding site for tubercle bacillus 10 (TB10; also known as CFP-10) protein. Overexpression of the

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(A)

Normal TMOD1 overexpression

(B)

TMOD1 downregulation Normal TMOD1 overexpression

Fig. 2. Roles of TMOD1 in neurons. (A) Overexpression of TMOD1 promotes neurite formation. (B) Overexpression of TMOD1 enhances thin spine formation, while its downregulation suppresses spine development.

TB10 protein in ovarian cancer cells disrupts filamentous actin stress fibers and induces a high rate of apoptosis [46]. When *TMOD1* is overexpressed, it interacts with TB10, thereby restoring the actin structure and effectively blocking TB10-dependent apoptosis. These results, therefore, indicate that the dynamic balance between actin, TB10, and TMOD1 regulates apoptosis homeostasis (Fig. 3) [9].

In regard to neuroblastoma, there is a correlation between the expression level of the *TMOD1* gene and the prognosis of neuroblastoma. Patients with neuroblastoma and high *TMOD1* gene expression have higher survival rates and better prognoses [47]. Cell experiments have shown that *TMOD1* overexpression in neuroblastoma cells leads to cell cycle arrest, reduced cell proliferation, and neuroblastoma cell differentiation [47]. Conversely, knocking down *TMOD1* can induce the loss of mature neuron marker expression and incomplete cell differentiation [47]. Analysis of clinical databases on cervical cancer revealed a correlation between the expression level of *TMOD1* and the disease survival rate [48]. Low *TMOD1* expression was associated with higher pathological grades and stages, whereas high expression correlates with lower pathological grades [48]. The knockdown of *TMOD1* in cervical cancer cells facilitated the G1/S phase transition of the cell cycle, suggesting a regulatory role for TMOD1 in cell cycle progression [48].

TMOD1 polymorphisms, such as rs10982622, have been found to significantly reduce thyroid cancer risk [49]. In breast cancer, NF-kappa-B (NF-κB)-induced upregulation of *TMOD1* expression leads to β-catenin accumulation in the nucleus, subsequently promoting cancer growth through matrix metallopeptidase 13 (MMP13) activation via the NF-κB–TMOD1–β-catenin–MMP13 axis [50]. Furthermore, *TMOD1* overexpression correlates with increased regional lymph node metastasis in oral cancer [51], and it has been identified as a potential risk gene for esophageal adenocarcinoma [52]. In regard to bladder cancer, *TMOD1* expression positively correlates with immune cell infiltration, suggesting its role in immune modulation and highlighting its potential as a biomarker for clinical screening [53].

TMOD1 and kidney

The expression of *TMOD1* is also found in the renal distal tubules and collecting ducts, and is involved in regulating water homeostasis [54,55]. Proteomic and bioinformatics analyses further implicated TMOD1 in multiple biological processes, including protein phosphorylation and metabolic regulation [54].

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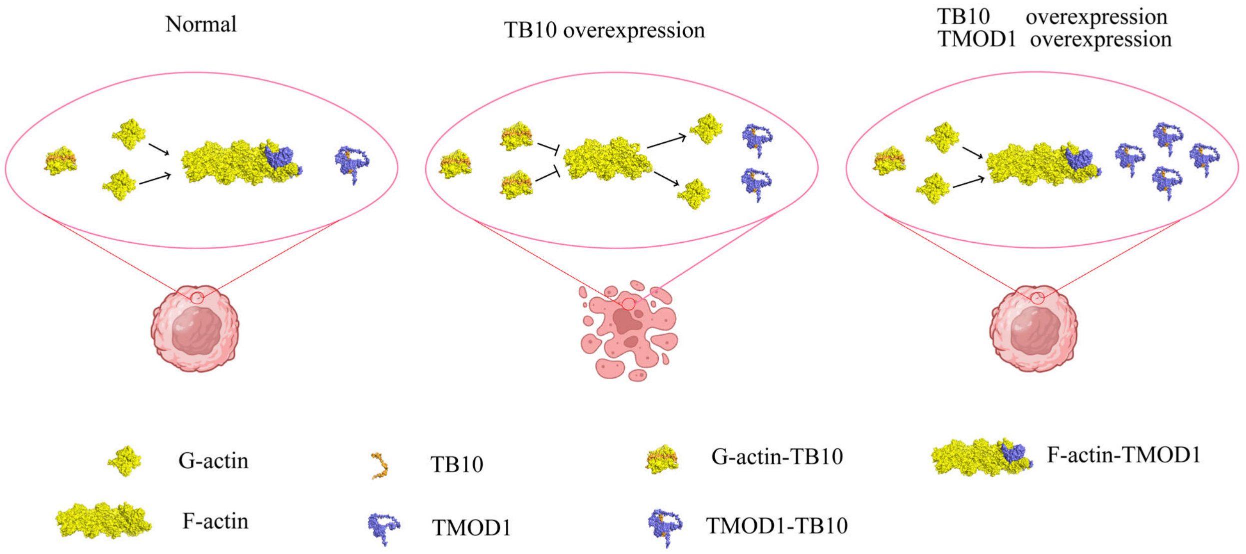

Fig. 3. Roles of TMOD1 in ovarian cancer. In ovarian cancer cells, overexpression of TB10 disrupts the binding of TMOD1 to actin, resulting in aberrant filamentous actin structures and induction of apoptosis. Overexpression of TMOD1 can rescue the effect induced by TB10 in ovarian cancer.

Manipulation of *TMOD1* expression in mouse kidney cells alters total cellular protein levels, particularly those of cyclin-dependent kinase 1 (CDK1). Overexpression of *TMOD1* increased CDK1 protein levels, whereas *TMOD1* knockdown reduced CDK1 levels, indicating a positive correlation between *TMOD1* expression and CDK1 regulation [55]. This evidence suggests the involvement of TMOD1 in urine concentration mechanisms [56], although further investigation of TMOD1 protein specificity in urine concentration is warranted.

Conclusions

The TMOD family is a well-known conserved protein family capable of binding to the slow-growing ends of filamentous actin. This phenomenon is closely related to actin dynamics. Actin is a protein with multiple functions that is widely expressed in cells. Actin is the most important cytoskeletal protein and is crucial for the formation and dynamic changes of the cytoskeleton. Therefore, TMOD1 is crucial for the cytoskeleton and morphology of cells as well as for the normal function of tissues and organs.

With the discovery of actin within the nucleus, its multiple functions have become a popular research topic [57]. Studies have shown that nuclear actin participates in various functions, including cell cycle regulation and DNA repair [58]. As an actin-binding protein, the protein sequence of TMOD1 contains a nuclear localization signal (NLS). Previous studies have confirmed that TMOD1 enters and exits the nucleus to regulate the expression of certain genes. In myogenic cells, nuclear TMOD1 may influence the differentiation process [59]. Actin-binding proteins are essential for actin filament dynamics, and over 160 actin-binding proteins have been identified. They are closely associated with various human diseases, including aging and cancer [60]. The $TMOD1^{R189W}$ mutation has recently been identified as a causative factor in familial cardiomyopathy [22]. The $TMOD1^{R189W}$ mutant protein still localizes correctly to the pointed ends of thin filaments and does not alter the gross formation or structure of the sarcomere, but it exhibits impaired actin filament capping activity. Overexpression of wild-type TMOD1 shortened thin filament length in rat cardiomyocytes, whereas excess $TMOD1^{R189W}$ failed to produce a similar effect, indicating that the mutation disrupts the role of TMOD1 in regulating actin filament length [22]. Beyond disrupting TMOD1 structure, mutations in its binding partners that impair their interactions also contribute to disease pathogenesis. For example, the $TPM1.1^{K15N}$ mutation reduces its affinity for TMOD1 and impairs actin filament pointed-end capping by TMOD1, without affecting TMOD1 localization to actin pointed ends [61,62]. The $TPM1.1^{K15N}$ mutation is confirmed to be associated with dilated cardiomyopathy [63]. Two mutants of TPM3.12, $TPM3.12^{A4V}$ and $TPM3.12^{R91C}$, have been implicated in congenital

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myopathy [10]. The A4V mutation is situated within the TMOD-binding domain of TPM3.12, whereas the R91C mutation lies in the actin-binding domain. The R91C variant also impairs the capping function of TMOD1 by reducing the affinity of $TPM3.12^{R91C}$ for TMOD1. Both point mutations alter actin filament length and disrupt muscle contraction, ultimately leading to muscle weakness and congenital myopathy. However, they function via distinct underlying molecular mechanisms [10]. These evidences further underscore the functional significance of the TMOD1–TPM interaction in maintaining normal biological function.

Several drugs targeting actin-binding proteins have been developed to treat actin-related diseases [64–66]. Although actin-binding proteins have shown potential as targets for different diseases owing to their wide involvement in many key cellular functions, the clinical detection and therapeutic potential of actin-binding-protein-related diseases in the future are enormous. As a member of the actin-binding protein family, mutations in TMOD1 are linked to abnormal spine formation and familial cardiomyopathy [22,42,43]. These established disease associations underscore its significance as a potential drug target. Meanwhile, the function, mechanism of action, and clinical relevance of TMOD1 require further investigation.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

YL and XP wrote the original draft; ZG and LZ produced the graphics; and PM and FL edited the review draft.

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