Role of CMTM6 in disease pathogenesis and clinical translation potential (Review)

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Received February 13, 2026; Accepted June 24, 2026

DOI: 10.3892/mmr.2026.13977

Abstract. The chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing (CMTM) family belongs to the human CKLF gene superfamily, which comprises CKLF and CMTM1-8. Among its members, CMTM6 encodes a protein exhibiting structural and functional characteristics that lie between classical chemokines and tetraspanins. CMTM6 is expressed in several normal tissues, including those of the immune, reproductive and nervous systems. Notably, its expression is frequently upregulated across a broad spectrum of tumors including, but not limited to, carcinomas of the lung, liver and gastrointestinal tract. CMTM6 contributes to tumor proliferation, invasion and metastasis by inhibiting immune responses, facilitating immune evasion and inducing epithelial-mesenchymal transition, thereby influencing patient prognosis and survival outcomes. The present review systematically summarizes the molecular functions, mechanisms of action, disease-related expression patterns and clinical translational applications of CMTM6, aiming to provide novel clinical insights and to guide the development of CMTM6-targeted therapeutic strategies.

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Abbreviations: CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing 6; PD-L1, programmed death ligand 1; EMT, epithelial-mesenchymal transition; PFS, progression-free survival; TNBC, triple-negative breast cancer; HCC, hepatocellular carcinoma; CC, cervical cancer; GC, gastric cancer; PC, pancreatic cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LUSC, lung squamous carcinoma; OSCC, oral squamous cell carcinoma; GBM, glioblastoma; OS, overall survival; DED, dry eye disease; ENO-1, enolase-1; GSK3β, glycogen synthase kinase-3β; ECA, endocervical adenocarcinoma; MTM, macrotrabecular-massive; TME, tumor microenvironment; AAV, antibody-associated vasculitis

Key words: CMTM6, PD-L1, tumor, clinical translation

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1. Introduction

The chemokine-like factor (CKLF) MARVEL transmembrane domain-containing 6 (CMTM6) is a key member of the human CKLF gene superfamily, first identified by the Human Genetics Research Center at Peking University (Beijing, China) in 2003 (1-3). The CMTM6 gene is located on chromosome 3p22.3 and encodes a protein comprising 183 amino acids, characterized by a typical MARVEL domain (2). CMTM6 is expressed in several tissue types, with particularly high levels observed in immune-related organs, such as the lung, liver, spleen, lymph nodes and tonsils, as well as in reproductive tissues (4,5). Moreover, CMTM6 expression is upregulated during myelination, serving a critical role in the development of functional myelin and the enhancement of neural function (6,7). In neural cells, CMTM6 is localized on the cell membrane of axonal Schwann cells, where it participates in regulating the transmembrane transport of secretory proteins. Notably, it is the first myelin-associated protein identified to limit axon diameter (8).

CMTM6 is a tetrameric protein characterized by six transmembrane domains, two extracellular loop domains, and short N- and C-terminal regions containing MARVEL domains that extend into the cytoplasm (8). The MARVEL domain of CMTM6 serves a crucial role in numerous biological processes, including vesicular trafficking and tight junction

formation, and is implicated in the pathogenesis of multiple diseases (9). Additionally, the extracellular loops within the MARVEL domain are essential for binding programmed death ligand 1 (PD-L1) and CD58 (10-12). In recent years, emerging evidence has highlighted the involvement of CMTM6 in the pathogenesis and progression of tumors and immune-related diseases (13-15). Consequently, elucidating the signaling pathways, mechanisms of action and expression patterns of CMTM6 in these conditions offers promising novel opportunities for understanding disease mechanisms and developing targeted therapeutic strategies.

2. Mechanisms of action of CMTM6

Programmed cell death protein 1 (PD-1)/PD-L1 signaling pathway. CMTM6 is recognized as a key regulator of PD-L1 protein stability. By binding to PD-L1, it prevents lysosomal degradation, thereby increasing PD-L1 expression on the surface of tumor cells and facilitating tumor immune evasion (Fig. 1). This function, validated across multiple cancer types, represents one of the most well-established and critical biological roles of CMTM6 (4,16-18). Through positive regulation of PD-L1, CMTM6 markedly contributes to tumor progression and PD-L1 expression itself holds considerable clinical relevance in several malignancies (19-21). *In vitro* and *in vivo* studies have both reported that loss of CMTM6 markedly reduces PD-L1 levels, thereby alleviating suppression of tumor-specific T-cell activity (4,16). CMTM6 exhibits high specificity for PD-L1; its depletion decreases PD-L1 expression without affecting the surface levels or transcription of major histocompatibility class I molecules (22,23). Moreover, CMTM6 expression levels are notably positively associated with CD58. Under CMTM6-deficient conditions, the expression of T-cell activation-related markers, such as CD137 and IL-2, is markedly downregulated. Mechanistically, CMTM6 serves as a critical regulator of CD58 protein stability, physically interacting with CD58 on recycling endosomes and protecting it from lysosomal degradation, thereby maintaining its cell surface expression (24,25). However, PD-L1 and CD58 compete for binding to the MARVEL domain of CMTM6. When PD-L1 expression is upregulated, its competitive advantage displaces CD58 from CMTM6 binding, leaving CD58 unprotected and shunting it toward the lysosomal degradation pathway (10,24,25). Additionally, a study reported that Hsc70 competes with CMTM6 for binding to PD-L1, with both proteins sharing the same PD-L1 binding region (amino acids 161-241). Knockdown of CMTM6 enhances the interaction between Hsc70 and PD-L1, promoting PD-L1 degradation via the endosomal microautophagy pathway (26).

Other signaling pathways associated with CMTM6. Within the Wnt/β-catenin signaling pathway, CMTM6 interacts with membrane-bound enolase-1 (ENO-1), activating the AKT/glycogen synthase kinase-3β (GSK3β) axis and thereby modulating Wnt signaling. This mechanism is closely associated with the maintenance of cancer stem cells, epithelial-mesenchymal transition (EMT) and resistance to cisplatin (27). Furthermore, CMTM6 regulates the Wnt pathway via β-catenin and is positively associated with infiltration of $CD66b^+$ neutrophils (28). In the ERK1/2 signaling pathway, exosomal CMTM6 promotes ERK1/2 phosphorylation in macrophages, enhancing the expression of M2 macrophage markers such as IL-10, arginase-1 and CD163, thereby inducing M2 polarization (29). Concurrently, CMTM6 suppresses activation of the pRB/E2F pathway, leading to inhibition of hepatocellular carcinoma (HCC) cell proliferation, reduced colony formation and G_0/G_1 phase cell cycle arrest (30). Additionally, CMTM6 activates the MAPK signaling pathway while inhibiting MAPK/ERK phosphorylation, which collectively promotes cell proliferation, migration, invasion and EMT, and simultaneously suppresses sodium-iodide symporter expression and apoptosis (31).

The expression of CMTM6 is also closely associated with activation of the mTOR signaling pathway. Knockdown of CMTM6 results in the downregulation of key mTOR pathway proteins, including phosphorylated mTOR and phosphorylated p70S6 kinase (32). Conversely, overexpression of CMTM6 upregulates critical components of the PI3K/AKT/mTOR and MAPK pathways, such as PI3K, AKT, MEK and ERK, thereby stabilizing the HER2 protein and inhibiting its ubiquitination (33). In cervical cancer (CC), CMTM6 promotes EMT and metastasis through the MAPK JNK/p38 pathway, characterized by decreased E-cadherin and increased vimentin expression. Additionally, CMTM6 suppresses the proliferation of endocervical adenocarcinoma (ECA) through the p53 pathway (34,35). Previous studies that performed RNA sequencing on CMTM6-knockdown ECA cell lines reported that differentially expressed genes were notably enriched in the p53 signaling pathway. Subsequent *in vitro* functional assays demonstrated that small interfering RNA-mediated CMTM6 knockdown markedly promoted the proliferative capacity of ECA cells, and this effect was mediated through activation of the p53 pathway (34,35). Gene set enrichment analysis further revealed a positive association between high CMTM6 expression and activation of the IL-6-JAK-STAT3 signaling pathway, suggesting a role in inflammation-related signaling and indirect promotion of tumorigenesis (36). Moreover, CMTM6 has been reported to regulate C-C motif chemokine ligand (CCL)4 expression through the AKT/GSK3β/β-catenin pathway in a PD-L1-independent manner, indicating a distinct mechanism involved in tumor progression (Fig. 2) (37).

Mechanisms regulating CMTM6 expression. Research has reported that human antigen R (HuR) binds to AU-rich elements within the 3' untranslated region of CMTM6 mRNA, stabilizing the transcript and upregulating its expression (38). Further research has revealed that the cerebellar degeneration-related protein 1 transcript upregulates CMTM6, potentially by modulating the expression and/or activity of transcription factors essential for CMTM6 expression (39). Experimental evidence also suggests that WEE1 and ATM inhibitors reduce PD-L1 expression by downregulating CMTM6 (40). Concurrently, EMT transcription factors, particularly SNAIL, have been implicated in upregulating CMTM6 expression (41). Yamamoto *et al* (42) reported that the hepatitis B virus drug entecavir increased PD-L1 expression through upregulation of CMTM6. Additionally, tumor cells may transfer CMTM6 to surrounding cells via exosomes, thereby enhancing PD-L1 expression on tumor stromal cells, including immune cells (29). Furthermore, five microRNAs

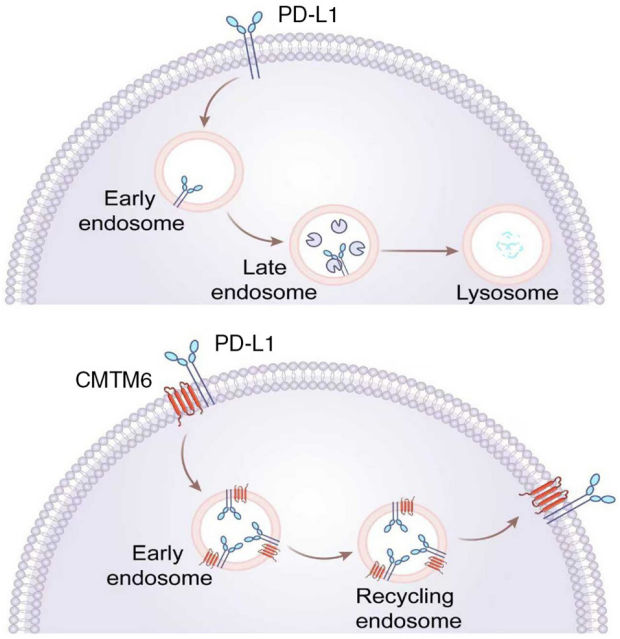

Figure 1. Intracellular trafficking of PD-L1 and regulation by CMTM6. CMTM6 interacts with PD-L1 in early and recycling endosomes, thereby inhibiting its lysosomal degradation. This interaction facilitates the recycling of PD-L1 to the plasma membrane, enhances surface PD-L1 expression, and serves a crucial role in tumor immune evasion. CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; PD-L1, programmed death ligand 1.

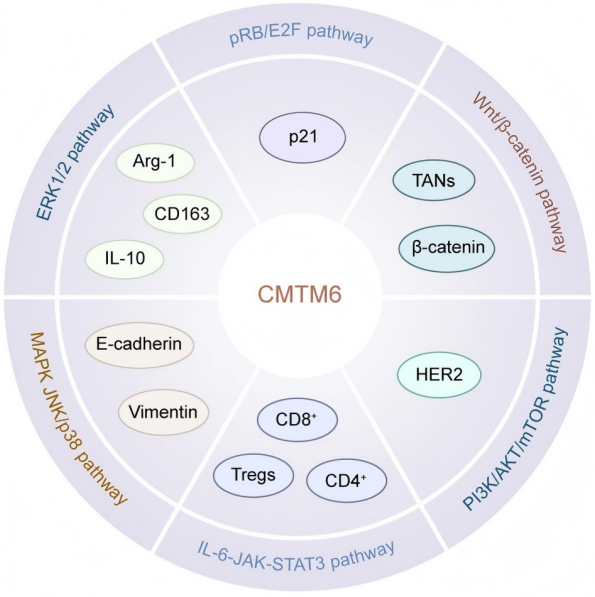

Figure 2. CMTM6 is involved in multiple signaling pathways and serves a multifaceted role in tumor development and prognosis. CMTM6 is implicated in the pRB/E2F pathway, p21-mediated cell cycle arrest epithelial-mesenchymal transition, and the regulation of various immunosuppressive factors, including Arg-1, CD163, IL-10, TANs and Tregs. Additionally, it influences $CD4^+$ and $CD8^+$ T-cell dynamics. Arg-1, arginase-1; CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; TANs, tumor-associated neutrophils; Tregs, regulatory T cells.

(miRs), including hsa-miR-545-5p and hsa-miR-514a-3p, have been reported to exhibit a notable negative association with CMTM6 expression (34). Transcription factors such as BCL3, CREB1 and FOXA1 are also predicted to suppress CMTM6 transcription, while E2F4 and ELK1 are potential activators of its expression (34).

In summary, CMTM6 is a widely expressed protein that serves crucial roles in tumor occurrence, development and treatment (24,33,34). It stabilizes PD-L1 and CD58 by protecting them from lysosomal degradation and extending their protein half-lives, thereby modulating the activation threshold of T cells. CMTM6 is also involved in multiple signaling pathways and is regulated at several levels by factors such as HuR, miRs, EMT transcription factors and antiviral therapeutics. Additionally, CMTM6 can be horizontally transferred via exosomes. Together, these mechanisms enable CMTM6 to promote tumor immune evasion and cancer progression, highlighting its potential as a promising target for cancer immunotherapy.

3. Expression of CMTM6 in diseases

CMTM6 and cancer. A comprehensive study integrating data from databases such as The Cancer Genome Atlas, Human Protein Atlas and The Cancer Proteome Atlas analyzed the expression patterns and genetic alteration profiles of CMTM6 across 33 cancer types, alongside its relationship with the tumor immune microenvironment (TIME) (Fig. 3) (43). The findings revealed that CMTM6 expression exhibits notable cancer type specificity and is closely associated with the TIME, particularly PD-L1 expression and immune cell infiltration. Moreover, CMTM6 demonstrated independent prognostic value in multiple types of cancer. These results highlight its potential as both a target for immunotherapy and a prognostic biomarker (Table I) (43).

CMTM6 in lung cancer. Lung cancer is one of the most prevalent and deadly malignancies worldwide, encompassing two primary categories: Small cell lung cancer (SCLC) and non-SCLC (NSCLC) (44,45). The development and progression of lung cancer involve complex signaling pathways that regulate key cellular processes, such as proliferation, survival, metastasis and therapeutic resistance (46). In NSCLC, CMTM6 expression is markedly elevated compared with that in normal tissues (47). Immunodetection studies have reported the presence of CMTM6 not only in cancer cells but also in tumor-associated macrophages, lymphocytes and adjacent bronchial epithelial cells (48,49). A retrospective analysis of patients with NSCLC revealed that CMTM6 expression exhibits histological subtype specificity in lung cancer, with notably higher levels in squamous cell carcinoma than in adenocarcinoma. Additionally, patients exhibiting high CMTM6 expression demonstrated a shorter overall survival (OS) time than those with low expression levels. Furthermore, CMTM6 expression was found to be elevated in cases with tumor-infiltrating lymphocytes (TILs) when compared to cases without such infiltration (47,50). In lung adenocarcinoma, CMTM6 is markedly upregulated and notably associated with advanced T stage and lymph node metastasis (36). In patients with lung squamous cell carcinoma (LUSC), CMTM6 expression has been reported to be positively associated with PD-L1 at both mRNA and protein levels. Furthermore, CMTM6 expression is positively associated with infiltration of $CD8^+$

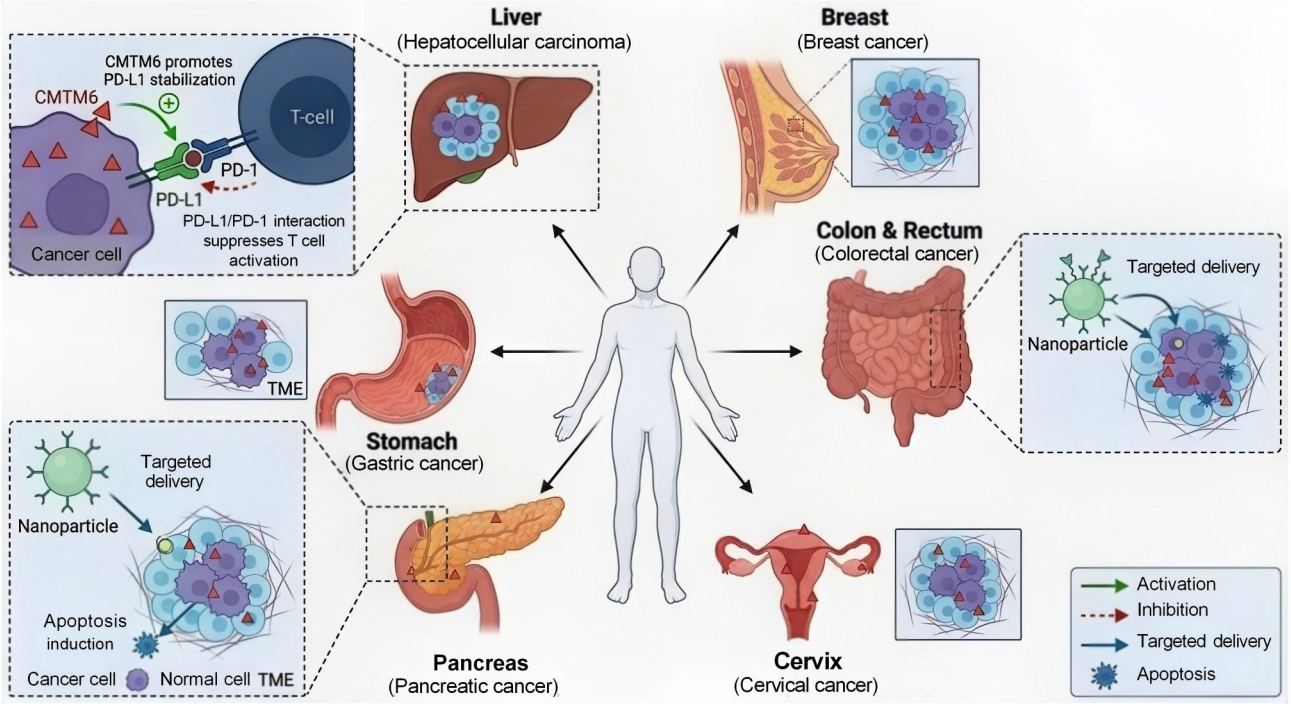

Figure 3. CMTM6-driven PD-L1 stabilization in multiple cancer types and nanoparticle-based targeted delivery strategy. CMTM6 enhances the stabilization of PD-L1 across various tumor types, including liver, breast, colorectal, gastric, pancreatic and cervical cancer. The increased levels of PD-L1 interact with PD-1 on T cells, leading to the suppression of T-cell activation. Additionally, the figure illustrates a nanoparticle system designed for targeted delivery to cancer cells within the TME, promoting apoptosis while sparing normal cells. CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TME, tumor microenvironment.

T cells, macrophages, neutrophils and dendritic cells, while it is negatively associated with $CD4^+$ T-cell infiltration, underscoring its notable role in modulating immune cell dynamics within the LUSC tumor microenvironment (TME) (51). Additionally, in SCLC, elevated CMTM6 expression has been reported in high-risk patient subgroups, suggesting its association with specific immune phenotypes and supporting its role as a novel independent prognostic factor (52).

CMTM6 in HCC. HCC, the most common form of primary liver cancer, poses a notable global health challenge due to its prolonged latency period and lack of distinct early symptoms, often resulting in late-stage diagnosis and high mortality rates (53-55). Numerous studies have reported that elevated CMTM6 expression in HCC is closely associated with tumor progression and poor prognosis. Increased CMTM6 levels are negatively associated with patient survival and positively associated with α-fetoprotein levels (15,56). Mechanistically, CMTM6 promotes tumor cell proliferation by activating the Wnt/β-catenin signaling pathway through stabilization of β-catenin (15). Moreover, CMTM6 facilitates the infiltration of tumor-associated neutrophils and synergizes with PD-L1 to regulate T cell-mediated immune responses (28). It also modulates the infiltration patterns of both $CD4^+$ and $CD8^+$ T cells within the TME (57). Clinically, high co-expression of CMTM6 and PD-L1 is associated with poor tumor differentiation, micro-intrahepatic metastasis, frequent recurrence, and consequently, shorter overall and recurrence-free survival in patients with HCC (58).

Moreover, CMTM6 promotes the proliferation and invasion of HCC cells by stabilizing vimentin, thereby inducing EMT (56). Elevated CMTM6 expression has been associated with increased Ki-67 levels and shorter recurrence-free survival (59). Additionally, CMTM6 promotes HCC recurrence by regulating the expression of B7 family ligands, suggesting its potential as both a biomarker for HCC recurrence risk and a therapeutic target (59). Furthermore, in the macrotrabecular-massive (MTM) subtype of HCC, co-expression of CMTM6 and PD-L1 is associated with higher inflammatory cell density and elevated PD-L1 expression, which corresponds with increased risks of HCC progression and mortality. An immune classification system based on CMTM6/PD-L1 co-expression effectively stratifies patients with MTM HCC by prognosis, highlighting the potential of CMTM6 as a biomarker and therapeutic target in HCC management (60). By contrast, Huang *et al* (30) and Zhu *et al* (61) reported low CMTM6 expression in HCC tissues, with higher CMTM6 levels associated with improved patient prognosis (30,61,62). Huang *et al* (30) reported that downregulation of CMTM6 in HCC cells reduced p21 levels, leading to activation of the pRB/E2F1 pathway and promoting G_1/S phase transition (Fig. 4).

Based on the relevant literature, three principal factors account for the discrepancies regarding CMTM6 in HCC. First, the etiological heterogeneity across cohorts, including variations in hepatitis virus type, the presence of cirrhosis, histological subtype and metabolic dysfunction-associated fatty liver disease, markedly influences the TIME. Second, CMTM6 exhibits bidirectional, context-dependent functions; it stabilizes PD-L1 to suppress antitumor immunity, binds to p21 to inhibit G_1/S transition, or interacts with vimentin to promote EMT, with the

Table I. Expression profile of CMTM6 in various types of cancer.

First author, year	Type of cancer	Proposed mechanism	Clinical sample validation	Experimental models	(Refs.)
Jia *et al*, 2023	Lung cancer	High CMTM6 expression activates the following: Angiogenesis, IL-6-JAK-STAT3, KRAS, PI3K-AKT-mTOR and TGF-β signaling pathways	Yes, n=110	Cell lines: A549, H358, Beas-2B	(36)
Gao *et al*, 2019	Lung cancer	CMTM6 promotes immune escape by stabilizing PD-L1	Yes, n=141	None (clinical trial)	(49)
Zugazagoitia *et al*, 2019	Lung cancer	CMTM6 expression is strongly positively associated with PD-L1 expression	Yes, n=180	None (clinical trial)	(50)
Koh *et al*, 2019	Lung cancer	PD-L1 expression is strictly dependent on the presence of CMTM6	Yes, n=123	None (clinical trial)	(48)
Kong *et al*, 2024	HCC	CMTM6 modulates the Wnt pathway by targeting β-catenin	Yes, n=60	Cell lines: HepG2, HuH-7, MHCC97H, LO2 Animal model: Nude mouse xenograft	(28)
Yugawa *et al*, 2021	HCC	CMTM6 extends the half-life of PD-L1, and thereby promotes EMT and the stemness phenotype	Yes, n=259	Cell lines: HuH-7/ Hep3B	(58)
Huang *et al*, 2022	HCC	CMTM6 binds to p21 and inhibits its ubiquitination, thereby suppressing activation of the pRB/E2F pathway	Yes, n=167	Cell lines: HepG2, Hep3B, HuH-7 Animal model: Nude xenograft	(30)
Huang *et al*, 2021	HCC	CMTM6 stabilizes vimentin to induce EMT, thereby promoting HCC metastasis	Yes, n=130	Cell lines: MHCC-97H, BEL-7402 HCCLM3 Animal model: Nude mouse xenograft.	(56)
Muranushi *et al*, 2021	HCC	CMTM6 promotes HCC recurrence by regulating the expression of B7 family ligands	Yes, n=84	Cell lines: PLC/PRF/5, Hep3B	(59)
Miao *et al*, 2023	Colorectal cancer	CMTM6 stabilizes CD58 protein by inhibiting its lysosomal degradation pathway	Yes, n=102	Cell lines: 8505C, A375, RKO, HAP1	(24)
Shaha *et al*, 2024	Colorectal cancer	CMTM6 forms a complex with Glut1 and Rab11, maintaining Rab11 mRNA level and activity to promote Glut1 membrane localization	No	Cell lines: HCT116, KM12L4, MC38 Animal model: Nude mouse xenograft. C57BL/6 syngeneic mouse model	(71)
Peng *et al*, 2021	Colorectal cancer	CMTM6 expression is positively associated with $CD4^+$ and $CD8^+$ T-cell infiltration	Yes, n=286	None (clinical trial)	(67)
Wu *et al*, 2021	Colorectal cancer	CMTM6 expression is positively associated with $CD163^+$ M2 macrophage density	Yes, n=32	None (clinical trial)	(68)

Table I. Continued.

First author, year	Type of cancer	Proposed mechanism	Clinical sample validation	Experimental models	(Refs.)
Li *et al*, 2022	Colorectal cancer	CMTM6 may modulate the immune microenvironment via the Wnt/β-catenin pathway	Yes, n=704	None (clinical trial)	(69)
Zhang *et al*, 2021	Gastric cancer	Knockdown of CMTM6 leads to decreased PD-L1 expression	Yes, n=185	None (clinical trial)	(76)
Li *et al*, 2020	Gastric cancer	CMTM6 expression is strongly positively associated with PD-L1 expression	Yes, n=122	None (clinical trial)	(74)
Nishi *et al*, 2021	Gastric cancer	CMTM6 promotes immune escape by stabilizing PD-L1	Yes, n=105	None (clinical trial)	(75)
Gao *et al*, 2023	Pancreatic cancer	CMTM6 enhances cell proliferation, migration and invasion by stabilizing PD-L1	Yes, n=179	Cell lines: AsPC-1, PANC-1	(80)
Huang *et al*, 2022	CC	CMTM6 promotes EMT and metastasis through the MAPK (JNK/p38) pathway	Yes, n=306	Cell line: CC epithelial cells Animal models: Subcutaneous transplanted tumor model, experimental lung metastasis model	(34)
Liang *et al*, 2023	CC	CMTM6 suppresses ECA proliferation through the p53 pathway	Yes, n=241	Cell line: HeLa, SiHa Animal model: Female BALB/c nude mice	(35)
Ma *et al*, 2023	CC	CMTM6 promotes immune escape by stabilizing PD-L1	Yes, n=102	None (clinical trial)	(83)
Yin *et al*, 2025	CC	Exosomal transfer of CMTM6 to macrophages induces M2a polarization via mTOR activation, leading to C-C motif chemokine ligand 2-mediated promotion of colorectal cancer progression	Yes, n=30	Cell lines: TC-1, HeLa, SiHa Animal models: Subcutaneous transplanted tumor model, experimental lung metastasis model	(13)
Xing *et al*, 2023	Breast cancer	CMTM6 stabilizes HER2 protein by inhibiting its ubiquitination	Yes, n=76	Cell lines: SKBR3, JIMT-1, BT-474 Animal model: Nude mouse xenograft	(33)
Xiao *et al*, 2021	Breast cancer	EMT regulates PD-L1 expression by inducing CMTM6 and CMTM7	Yes, n=299	Cell lines: MCF-7, MDA-MB-231	(41)
Xiao *et al*, 2022	Breast cancer	SNAI1-induced EMT upregulates PD-L1 and CMTM6/7 synchronously in MCF-7 mesenchymal cells	No	Cell lines: MCF-7, MDA-MB-231	(88)
Zheng *et al*, 2020	OSCC	CMTM6 promotes tumorigenesis by inducing NRP1 expression	Yes, n=244	Cell lines: HN4, HN6, HOK Animal model: Nude mouse xenograft model	(93)
Pang *et al*, 2021	OSCC	Exosomal CMTM6 from OSCC activates the ERK1/2 signaling pathway, inducing M2 macrophage polarization	Yes, n=45	Cell lines: Cal-27, SCC25, THP-1 Animal model: 4NQO-induced OSCC mouse model	(29)

Table I. Continued.

First author, year	Type of cancer	Proposed mechanism	Clinical sample validation	Experimental models	(Refs.)
Martinez-Morilla *et al*, 2020	Melanoma	CMTM6 expression is strongly positively associated with PD-L1 expression	Yes, n=60	Cell lines: CD68 macrophages, CD3 T cells, CD20 B cells	(98)
Miao *et al*, 2023	Melanoma	CMTM6 positively regulates CD58 expression, while CD58 and PD-L1 exhibit competitive binding to the CMTM6 MARVEL domain	Yes, n=88	Cell lines: 8505C, A375, RKO, HAP1 Animal models: *in vivo* xenograft models	(24)
Xue *et al*, 2022	Glioma	CMTM6 expression is strongly positively associated with PD-L1 expression	Yes, n=177	None (clinical trial)	(101)
Wei *et al*, 2022	Glioma	Knockdown of CMTM6 down-regulates key proteins in the mTOR pathway, leading to cell cycle arrest at the G_1/G_0 phase	Yes, n=44	Cell lines: U87, U251, T98G, U373, HEB Animal model: Nude mouse xenograft model	(32)
Li *et al*, 2025	Glioma	CMTM6 inhibits antigen presentation by stabilizing PD-L1 and promoting M2 polarization	No	Cell line: HMC3 human microglial cells Animal model: GL261 syngeneic mouse model of glioblastoma	(103)
Yin *et al*, 2022	Ovarian cancer	CMTM6 expression is positively associated with $CD4^+$ T-cell and neutrophil infiltration	No	Cell lines: IOSE80, A2780, ES2, Hey, SKOV3	(104)
Wang *et al*, 2022	Clear cell renal cell carcinoma	CMTM6 deficiency induces DNA damage and consequently causes cell cycle arrest at the G_2/M phase	Yes, n=144	Cell lines: HKC, A498, Caki-1, SN12-PM6 Animal models: Mouse orthotopic syngeneic graft and xenograft renal cancer model	(107)
Ishihara *et al*, 2021	Undiffe rentiated pleomor-phic sarcoma	CMTM6 expression is strongly positively associated with PD-L1 expression	Yes, n=51	Cell line: CD8 T cells	(108)
Chen *et al*, 2024	Thyroid cancer	CMTM6 promotes cell proliferation, migration, invasion and EMT via MAPK pathway activation, while suppressing NIS expression and apoptosis	No	Cell lines: TEC, FTC133, BCPAP, TPC-1, SW1736	(31)
Zwick *et al*, 2025	Acute leukemia	CMTM6 is stabilizied by the FLT3-ITD mutation via protein interaction, reducing its lysosomal and proteasomal degradation	Yes, n=15	Cell lines: MV4-11, Ba/F3, 32D, WEHI-3B Animal models: Allogeneic hemato-poietic cell transplan-tation model, MV4-11 xenograft model	(14)

CC, cervical cancer; CMTM, chemokine-like factor-like MARVEL transmembrane domain-containing protein; ECA, endocervical adenocarcinoma; EMT, epithelial-mesenchymal transition; Glut1, glucose transporter 1; HCC, hepatocellular carcinoma; NIS, sodium-iodide symporter; NRP1, neuropilin-1; OSCC, oral squamous cell carcinoma; PD-L1, programmed death ligand 1.

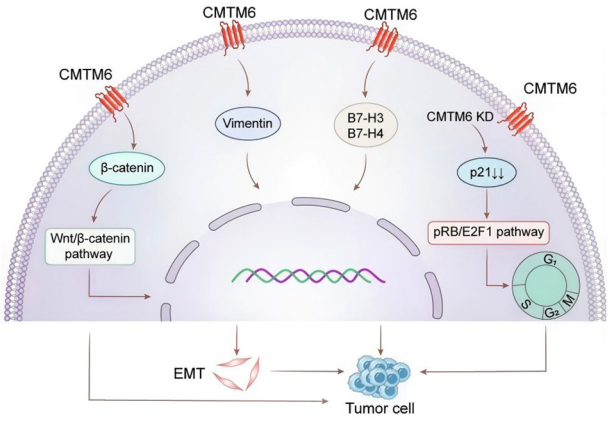

Figure 4. Schematic illustration of the mechanisms of CMTM6 in HCC. CMTM6 regulates the Wnt signaling pathway through β-catenin and stabilizes vimentin, thereby inducing EMT and promoting metastasis in HCC. Furthermore, CMTM6 facilitates HCC recurrence by modulating the expression of B7 family ligands. Conversely, the downregulation of CMTM6 results in decreased levels of p21, which activates the pRB/E2F1 pathway and subsequently promotes the G_1/S phase transition in HCC cells. CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; KD, knockdown.

net effects varying according to the molecular partner involved. Third, the complexity of TIME further diversifies the observed outcomes. Wei *et al* (32). reported that the co-expression of CMTM6 and PD-L1, along with $CD4^+$ T-cell infiltration, was associated with a favorable prognosis, whereas Kong *et al* (28) revealed that CMTM6 can promote tumor-associated neutrophil infiltration through the Wnt/β-catenin pathway, which is associated with a poor prognosis. Furthermore, differences among studies regarding sample size, clinical stage distribution, detection methodologies and assessment criteria may contribute to the inconsistent conclusions.

CMTM6 in colorectal cancer (CRC). CRC ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide (63,64). Its complexity is driven by diverse signal transduction networks that regulate cellular proliferation, survival, differentiation and apoptosis (65). CMTM6 expression has been reported to be elevated in CRC tissues compared with that in matched normal tissues, with high CMTM6 levels associated with increased PD-L1 expression and greater immune cell infiltration (66). Notably, CMTM6 levels tend to be lower in advanced-stage CRC tumors compared with those in early-stage tumors. High CMTM6 expression is associated with lower pathological T stage and increased density of TILs, suggesting a notable role for CMTM6 in modulating the TIME (67). Moreover, Wu *et al* (68) reported that in patients with rectal cancer undergoing PD-1/PD-L1 inhibitor therapy, CMTM6 expression in M2 macrophages can serve as a promising biomarker for predicting treatment response. Furthermore, an immunohistochemical analysis of a tissue microarray from 704 patients with CRC assessing β-catenin, CMTM6, PD-L1 and mismatch repair protein expression revealed a positive association between CMTM6/PD-L1 co-expression and β-catenin levels, suggesting that CMTM6/PD-L1 may influence the immune microenvironment via the Wnt/β-catenin signaling pathway (69).

Liver metastasis of CRC is a major contributor to CRC-related mortality (70). A study reported that CMTM6 promotes CRC liver metastasis by mediating the Warburg effect. Mechanistically, CMTM6 forms a complex with glucose transporter 1 (Glut1) and Rab11 in the endoplasmic reticulum, facilitating Rab11-dependent trafficking of Glut1 to the plasma membrane, which enhances glucose uptake and glycolysis (71). CMTM6 serves a critical role in sustaining CRC cell cycle progression and liver metastasis, contrasting with its function in HCC, where it suppresses G_1 to S phase transition by stabilizing p21 and inactivating the pRB/E2F pathway (30).

CMTM6 in gastric cancer (GC). GC is a complex and heterogeneous disease characterized by marked phenotypic and genetic variability (72). Studies have reported that CMTM6 expression is markedly elevated in GC tissues compared with that in normal gastric tissues, with even higher levels observed in advanced-stage disease (73). Immunohistochemical analysis of 122 postoperative GC tissue specimens revealed a notable association between CMTM6 and PD-L1 protein expression (74). A retrospective study involving 105 patients with stage II/III GC performed by Nishi *et al* (75) reported markedly lower 5-year OS and disease-free survival rates in the CMTM6 high-expression group compared with that in the low-expression group, supporting the role of CMTM6-mediated immune escape via PD-L1 (75). Furthermore, immunohistochemical staining of 185 GC specimens from radical gastrectomies indicated that high co-expression of CMTM6 and PD-L1 was notably associated with Borrmann type, lymph node metastasis, peritoneal metastasis and Tumor-Node-Metastasis stage, but showed no association with patient age, sex, tumor size, differentiation grade, tumor location or T stage. Survival analysis further demonstrated that high CMTM6 expression was associated with a shorter OS and worse prognosis, with the worst outcomes observed in cases with concomitant high PD-L1 expression (76). Additionally, in gastric adenocarcinoma, CMTM6 expression has been shown to be higher in tumor tissues than in adjacent normal tissues, and to be positively associated with PD-L1 expression in both epithelial and stromal compartments. CMTM6 expression also showed positive associations with tumor burden and the Ki-67 proliferation index, indicating that membrane co-expression of CMTM6 and PD-L1 on tumor epithelial cells serves as a marker of poor prognosis in gastric adenocarcinoma (77).

CMTM6 in pancreatic cancer (PC). PC remains one of the most lethal malignancies worldwide, with limited advances in effective treatments over recent decades (78,79). Notably, studies have identified upregulated CMTM6 expression in pancreatic adenocarcinoma tissues (40,80). Functional analyses have demonstrated that CMTM6 promotes the proliferation, migration and invasion of PC cells (80). CMTM6 expression has also been reported to be positively associated with PD-L1 levels, and CMTM6 has been shown to co-immunoprecipitate with PD-L1 protein in PC cell lines. Upregulation of CMTM6 contributes to shaping an inflammatory TME characterized by a heightened immune response (80). Furthermore, research has indicated that inhibition of WEE1, alone or in combination with ATM inhibition, downregulates PD-L1 expression by blocking phosphorylation of GSK3β at serine 9 and reducing CMTM6 levels. In Capan-1 mouse xenograft models, treatment

with AZD1775 (a WEE1 inhibitor) combined with AZD0156 (an ATM inhibitor) has been shown to reduce tumor growth and downregulate the expression of PD-L1, CMTM6, CD163 and CXCR2 in tumors, factors known to contribute to tumor immune evasion (40).

CMTM6 in CC. CC, primarily driven by human papillomavirus infection, is considered preventable and manageable due to its well-established etiology (81,82). CMTM6 serves a critical role in CC, with its expression closely associated with the biological behavior of the tumor. Studies have reported that CMTM6 expression is markedly upregulated in CC tissues compared with that in adjacent non-cancerous tissues, and positively associated with PD-L1 expression. This co-expression is strongly associated with poor patient prognosis (13,83). *In vitro* experiments have demonstrated that CMTM6 promotes invasion, migration, proliferation and EMT of CC cells by activating the MAPK JNK/p38 signaling pathway (34). Conversely, CMTM6 inhibits the proliferation of ECA cells through the p53 pathway and recruits T cells, thereby enhancing the antitumor immune response (35). The multiple molecular functions of CMTM6 underpin its dual role; it stabilizes PD-L1 to suppress antitumor immunity, binds to p21 to inhibit G_1/S transition, or interacts with vimentin to promote EMT, with the net effects varying according to the molecular partner involved.

Within the TIME, CMTM6 expression has been reported to be positively associated with immune checkpoint components. Silencing CMTM6 increases infiltration of $CD8^+$ and $CD4^+$ T cells while reducing the proportion of exhausted T cells (84). Moreover, soluble CMTM6 levels are markedly elevated in the plasma of patients with CC and are positively associated with exosomal PD-L1, suggesting a role for CMTM6 in tumor immune evasion via the exosomal pathway (85). A recent study further reported that exosomes secreted by CC cells carry CMTM6, which activates the mTOR signaling pathway in macrophages, inducing M2a polarization. These M2a macrophages subsequently secrete CCL2, enhancing the migration and invasion of CC cells, and promoting disease progression (13). Collectively, these findings highlight CMTM6 not only as a potential prognostic biomarker for CC but also as a promising target for immunotherapy.

CMTM6 in breast cancer. Breast cancer is the most common malignancy among women worldwide. Triple-negative breast cancer (TNBC), which accounts for 10-20% of all breast cancer cases, is an aggressive subtype associated with a poor prognosis (86). A study reported that CMTM6 expression is markedly higher in patients with TNBC compared with that in those with HER2-positive breast cancer (87). Moreover, elevated CMTM6 levels are associated with shorter progression-free survival (PFS) in patients with TNBC, and multivariate Cox regression analysis has identified CMTM6 as an independent risk factor for PFS (87). Furthermore, CMTM6 expression has been reported to be positively associated with both the EMT score in breast cancer cell lines and the key EMT marker vimentin in TNBC (41). In SNAI1-induced MCF-7 cells (MCF-7-Mes), acquisition of a mesenchymal phenotype leads to increased PD-L1 and CMTM6 expression. Silencing CMTM6 in MCF-7-Mes cells partially reduces PD-L1 surface expression, indicating that PD-L1 expression is partially dependent on CMTM6. Furthermore, dual knockdown of CMTM6 and CMTM7 markedly decreases PD-L1 surface expression, suggesting that these proteins cooperatively regulate PD-L1 levels (41,88). Additionally, research has reported that hsa_circ_0067842 upregulates CMTM6 expression via HuR, while knockdown of HuR reduces CMTM6 mRNA stability. These findings establish the hsa_circ_0067842/HuR/CMTM6/PD-L1 axis as a potential prognostic biomarker and therapeutic target for breast cancer immunotherapy (89).

CMTM6 in oral squamous cell carcinoma (OSCC). OSCC, the predominant subtype of head and neck squamous cell carcinoma, has a 5-year survival rate of <50%, with its precise etiology still unclear (90-92). CMTM6 holds notable clinicopathological relevance in OSCC, as its high expression is closely associated with tumor progression and poor prognosis. A study reported that both CMTM6 and neuropilin-1 (NRP1) are upregulated in OSCC tissues and physically interact. NRP1 contributes to the degradation of CMTM6, while CMTM6 promotes tumorigenesis by inducing NRP1 expression (93). Furthermore, CMTM6 expression is positively associated with PD-1 and PD-L1 levels, suggesting a potential synergistic role in immune pathways that facilitate tumor immune escape in OSCC (94). CMTM6 can also be transferred to macrophages via exosomes, where it activates the ERK1/2 signaling pathway and induces M2 macrophage polarization, thereby promoting malignant progression of OSCC (95). Additionally, research has shown that CMTM6 interacts with membrane-bound ENO-1 to activate the AKT/GSK3β axis, which modulates the Wnt signaling pathway, driving EMT and cisplatin resistance (27). Thus, CMTM6 not only regulates tumor cell behavior in OSCC but also markedly influences the immune microenvironment, underscoring its potential as a therapeutic target (Fig. 5).

CMTM6 in melanoma. Melanoma, which arises from melanocytes, is the most lethal form of skin cancer (96,97). In melanoma, CMTM6 expression has been reported to be markedly associated with several immune markers, including PD-L1, CD3, CD20 and CD68. Furthermore, high CMTM6 expression within stromal and immune compartments has been shown to be significantly associated with improved survival following immunotherapy (P=0.007) and demonstrates notable prognostic value in multivariate analyses (98). Furthermore, high co-expression of CMTM6 and PD-L1 in the stromal compartment has been significantly associated with prolonged survival (P=0.028), highlighting CMTM6 as a potential predictive biomarker for immune checkpoint inhibitor therapy (98). Further studies have reported that CMTM6 is essential for maintaining CD58 stability in melanoma, where intact CD58 expression and its interaction with CD2 are critical for effective antitumor immunity. When CD58 is lost, CMTM6 facilitates PD-L1 upregulation, thereby promoting immune evasion. The competitive interactions among CMTM6, CD58 and PD-L1 regulate their endosomal recycling and lysosomal degradation rates, establishing a molecular mechanism by which cancer cells balance immunosuppressive and immunostimulatory signals (10). Collectively, these findings underscore the marked role of CMTM6 in melanoma immunotherapy, positioning it as both a promising prognostic biomarker and therapeutic target.

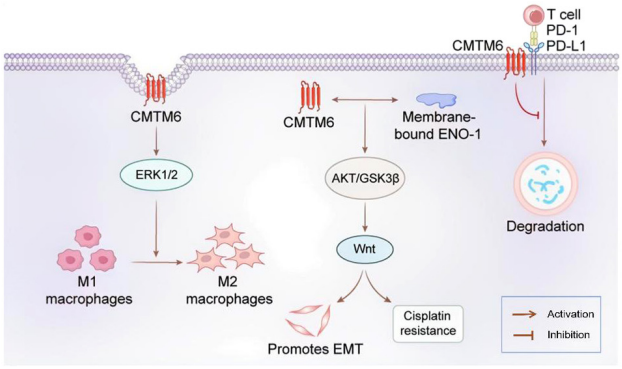

Figure 5. Mechanisms of CMTM6 action in oral squamous cell carcinoma. CMTM6 can be transferred to macrophages via exosomes, where it activates the ERK1/2 signaling pathway and induces M2 macrophage polarization. Additionally, CMTM6 interacts with membrane-bound ENO1 to activate the AKT/GSK3β axis, which modulates the Wnt signaling pathway, thereby driving EMT and contributing to cisplatin resistance. Furthermore, CMTM6 maintains PD-L1 expression on the surface of tumor cells by inhibiting its lysosomal degradation. By stabilizing PD-L1, CMTM6 facilitates the binding of PD-L1 to PD-1 on T cells, thus suppressing T-cell activation. CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; EMT, epithelial-mesenchymal transition; ENO-1, enolase-1; GSK3β, glycogen synthase kinase-3β; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

CMTM6 in glioma. Glioma is the most prevalent and aggressive malignant brain tumor in adults, posing notable challenges in oncology due to its rapid progression, therapeutic resistance and poor prognosis (99,100). In glioma, CMTM6 expression is closely associated with several biological processes and therapeutic responses. A study reported that both CMTM6 and CMTM4 are markedly associated with PD-L1 expression in glioma, with macrophages identified as the primary cell type expressing these proteins. High expression levels of CMTM6 and CMTM4 are associated with reduced OS, suggesting their potential as biomarkers for immune-targeted interventions in glioma (101). Moreover, elevated CMTM6 expression in glioma has been associated with poor prognosis. Knockdown of CMTM6 inhibits the proliferation, invasion and migration of U87 and U251 glioma cells, increases apoptosis rates, inactivates the mTOR signaling pathway, and reduces tumor volume and Ki-67 expression (32). CMTM6 is highly expressed in glioma and is strongly associated with the TIME and inflammatory responses (102). A recent study further demonstrated that CMTM6 is markedly upregulated in high-grade glioma and associated with poor patient outcomes. CMTM6 knockout resulted in downregulation of PD-L1 and TGFβ1/2/3, alongside upregulation of pro-inflammatory factors IL-6 and CCL3, promoting microglial polarization toward the M1 phenotype and thereby modulating the immune microenvironment (103). Collectively, these findings underscore the crucial role of CMTM6 in glioma pathogenesis, progression and immune regulation, highlighting its potential as both a diagnostic biomarker and therapeutic target.

CMTM6 in other types of cancer. Beyond the aforementioned malignancies, CMTM6 serves pivotal roles in several other tumors, with its functional impact and mechanisms differing across cancer types. In ovarian cancer, the most lethal gynecological malignancy, CMTM6 upregulation is paradoxically associated with a more favorable prognosis. This may be attributed to its modulation of immune cell infiltration and the expression of immune cell markers, with copy number variations and DNA methylation implicated in its aberrant expression (104-106). In clear cell renal cell carcinoma, CMTM6 depletion has been reported to notably inhibit cell proliferation, migration and invasion, while enhancing antitumor immunity, evidenced by increased infiltration of $CD4^+$ and $CD8^+$ T cells. Loss of CMTM6 also induces a DNA damage response, leading to cellular senescence and secretion of inflammatory factors (107). In undifferentiated pleomorphic sarcoma, CMTM6 expression has been reported to be strongly associated with high PD-L1 levels, and elevated expression is markedly associated with poor prognosis (108). In thyroid carcinoma, CMTM6 promotes the development of thyroid cancer by inhibiting sodium/iodide symporter activity through activating the MAPK signaling pathway, with its expression closely associated with tumor metastasis (31). In acute myeloid leukemia, FLT3-ITD mutations enhance CMTM6 protein stability through protein-protein interactions, thereby promoting PD-L1 expression and facilitating immune evasion (14). Collectively, these studies underscore the complex and diverse mechanisms through which CMTM6 influences tumor biology, emphasizing its potential as a therapeutic target across multiple cancer types.

CMTM6 in non-neoplastic diseases. Beyond its roles in oncology, CMTM6 has emerged as a key regulator in numerous non-neoplastic pathological conditions. In dry eye disease (DED), reduced CMTM6 expression is associated with increased disease severity. Its downregulation contributes to decreased tear secretion, corneal epithelial defects and heightened inflammatory responses, implicating the CMTM6-NF-κB p65 signaling axis as a potential therapeutic target for DED (109). In primary Sjögren's syndrome, CMTM6 levels are notably elevated in both the serum and labial salivary gland tissues of patients, and are positively associated with PD-1/PD-L1 levels, disease activity (as assessed by EULAR Sjögren's Syndrome Disease Activity Index) and immunological indices, including IgG and erythrocyte sedimentation rate. By contrast, serum CMTM6 levels are negatively correlated with lymphocyte counts and $CD3^+$ T cells (r=-0.397). These findings suggest that CMTM6 may participate in the PD-1/PD-L1 pathway by regulating PD-L1 stability, thereby influencing lymphocyte activation and peripheral immune tolerance (110). Additionally, in *Helicobacter pylori*-infected gastric mucosal cells, CMTM6 stabilizes PD-L1 protein by preventing its degradation. CRISPR/Cas9-mediated knockout of CMTM6 alters protein ubiquitination and affects the expression of cell surface receptors, highlighting its regulatory role in infection-associated immune modulation (111).

Furthermore, CMTM6 contributes to the pathogenesis of autoimmune diseases. In antineutrophil cytoplasmic antibody-associated vasculitis (AAV), reduced CMTM6 expression leads to increased lysosomal degradation of PD-L1, thereby impairing negative regulatory signaling in T cells. This suggests that targeting lysosomal function could offer a novel therapeutic approach for AAV (112). CMTM6 expression is also upregulated in neutrophils from patients with antiphospholipid syndrome (APS), and neutrophil extracellular traps

(NETs) serve a critical pathogenic role in thrombosis associated with APS. It is therefore hypothesized that CMTM6 may contribute to the pro-thrombotic process in APS by promoting or sustaining excessive neutrophil activation and enhancing NET release; however, the underlying molecular mechanisms, including the potential involvement of PD-L1 stabilization or other signaling pathways, remain to be elucidated (113,114). A recent study identified CMTM6 as a key regulator in the pathogenesis of rheumatoid arthritis (RA), acting through the CMTM6-TAK1-NF-κB/MAPK axis to modulate fibroblast-like synoviocyte function and macrophage polarization, thereby promoting RA progression. Targeting CMTM6 thus represents a potential therapeutic direction for RA, although the specific binding sites between CMTM6 and TAK1, as well as the particular ubiquitin ligases and deubiquitinases involved in regulating this axis, require further analysis (115). In summary, CMTM6 has emerged as a promising diagnostic and therapeutic target for several non-neoplastic diseases; however, the precise mechanisms by which CMTM6 influences the onset and progression of autoimmune disorders require further investigation.

4. CMTM6 and clinical translation

Cancer is a major global public health challenge. A critical mechanism of cancer immune evasion involves immune checkpoint molecules, and leveraging the immune system to combat malignant tumors has become a central focus in cancer therapy. CMTM6 serves a pivotal role in the treatment of several types of cancer, primarily by stabilizing key proteins, regulating signaling pathways and modulating therapy resistance (Table II). In lung cancer, CMTM6 influences DNA double-strand break repair by regulating the nuclear translocation of PD-L1, thereby contributing to radiotherapy resistance (74). In NSCLC, CMTM6 co-localizes with EGFR in recycling endosomes, preventing its lysosomal degradation. Elevated CMTM6 expression is associated with resistance against tyrosine kinase inhibitors, and targeting CMTM6 effectively suppresses the proliferation of these resistant cancer cells (116).

In cisplatin-resistant OSCC, CMTM6 promotes chemoresistance by regulating ribosome biogenesis and the Wnt signaling pathway, while its inhibition restores cisplatin sensitivity (27,117). In pancreatic ductal adenocarcinoma (PDAC), CMTM6 forms a positive feedback loop with insulin-like growth factor 2 mRNA-binding protein 1, enhancing tumor stemness and contributing to gemcitabine resistance. Combining an EP300 inhibitor with gemcitabine effectively overcomes this resistance (118). A recent study on novel microbial immunotherapy for PDAC has characterized the tumor-targeting capability, immune-remodeling properties and safety profile of an attenuated *Salmonella typhimurium* strain, CRC2631, and its next-generation derivative, iSTORM. Notably, iSTORM exploits its bacterial carrier CRC2631 to selectively colonize PDAC tumors and locally deliver CMTM6-silencing short hairpin RNA. This then disrupts PD-L1 stability and inhibits myeloid-mediated immunosuppression, ultimately enhancing $CD8^+$ T-cell activation and antitumor function (119). In glioblastoma multiforme, elevated CMTM6 expression is closely associated with the TIME, promoting cell migration and EMT. Notably, the anticancer compound piperlongumine (PL) induces CMTM6 expression, but the deep mechanism of the relationship between PL and CMTM6 needs further study (120). Moreover, in renal cell carcinoma, CMTM6 expression is higher in immune cells than in tumor cells. It is also positively associated with PD-L1, and its elevated levels are associated with a shorter PFS in patients receiving nivolumab treatment (121).

In HER2-positive breast cancer, CMTM6 stabilizes the HER2 protein by inhibiting its ubiquitination, resulting in trastuzumab resistance. Knockdown of CMTM6 restores drug sensitivity and evidence suggests that combining trastuzumab-based therapies with CMTM6 inhibitors, such as rapamycin, lapatinib and pyrotinib, may enhance treatment efficacy (33). In TNBC, CMTM6 modulates docetaxel resistance through c-MYC-mediated ribosome biogenesis, while knockdown of circUBR5 enhances the activity of miR-340-5p and reduces the expression of CMTM6 and c-MYC, thereby improving chemosensitivity (122). Additionally, research has indicated that REIC/Dkk-3 competitively binds CMTM6, releasing PD-L1 and promoting its degradation, thereby suppressing tumor progression (123). A recent study reported that a novel anti-PD-L1 antibody (H1A) can disrupt the PD-L1-CMTM6 interaction, induce PD-L1 degradation, and enhance myeloid cell activation and cytotoxic T-cell expansion, improving therapeutic outcomes in tumors with limited responses to immune checkpoint inhibitors (124). Another study constructed a stable full-length membrane protein complex of CMTM6-PD-L1 using membrane simulation strategies. Based on this complex, an anti-CMTM6 nanobody, 1A5, was screened, which can reduce T cell immunosuppression *in vitro* and exerts its antitumor effect primarily through $CD8^+$ T cells in mouse models. This confirms that CMTM6 can serve as a novel target for antibody-mediated tumor immunotherapy (125). Notably, a study on the treatment of skin malignant melanoma found that by designing intermediate chimeric peptide (PEP)-PDL1, it could specifically bind to the PD-1 binding domain of PD-L1, rather than the Hsc70/CMTM6 binding domain, thereby avoiding competitive inhibition by CMTM6. Simultaneously, it binds to Hsc70, mediating the degradation of PD-L1 into lysosomes, thus restoring antitumor T-cell immunity in a B16F10-derived malignant melanoma mouse model (126).

In summary, targeting CMTM6 and its associated pathways may represent a potential therapeutic strategy for multiple cancer types. However, the translation of CMTM6-targeted therapy from basic research to clinical application faces several challenges. The first is off-target effects and safety concerns: CMTM6 is broadly expressed in normal tissues with a substrate spectrum extending beyond PD-L1, simultaneously stabilizing the inhibitory ligand PD-L1 and the co-stimulatory molecule CD58; non-selective inhibition may therefore compromise antitumor immunity. Moreover, strong and specific binding of CMTM6 to FAS has been observed in mouse models, enhancing the sensitivity of mouse cells to FAS ligand-induced cytotoxicity. However, in human cell-based studies, this interaction is absent for human FAS, which can be attributed to a three-amino-acid divergence at the boundary between the extracellular and transmembrane domains. This divergence disrupts the binding capacity, creating a species-specific translational pitfall (127). The second

Table II. Role of CMTM6 in cancer therapy.

First author/s, year	Cancer type	Mechanism	Methods	Drugs	Clinical trials	(Refs.)
Huang *et al*, 2022	*Hepatocellular carcinoma*	CMTM6 binds to p21 and inhibits its ubiquitination, thereby inducing G_0/G_1 phase arrest	Co-IP, ubiquitination assay, flow cytometry	Doxorubicin, cisplatin	No	(30)
Xia *et al*, 2025	Lung cancer	CMTM6 binds to EGFR and thereby inhibits its lysosomal degradation	Proteomic screening and *in vitro*/*in vivo* functional validation	Anti-CMTM6 nanobody (1A5)	Yes, n=92	(116)
Xing *et al*, 2023	Breast cancer	CMTM6 stabilizes the HER2 protein by inhibiting its ubiquitination-mediated degradation and activates downstream signaling	Ubiquitination assay and *in vitro*/*in vivo* functional validation	Trastuzumab	Yes, n=72	(33)
Mohapatra *et al*, 2021	Oral squamous cell carcinoma	CMTM6 activates Wnt signaling through the ENO-1/AKT/GSK3β axis, promoting cancer stem cell properties and drug resistance	Co-IP, IHC, immunofluorescence, RT-qPCR, RNA sequencing, *in vitro*/*in vivo* functional validation	Cisplatin	Yes, n=34	(27)
Zhu *et al*, 2024	Pancreatic ductal adenocarcinoma	EP300 mediates H3K27ac to activate CMTM6 transcription; CMTM6 subsequently stabilizes IGF2BP1 by inhibiting its ubiquitination	Co-IP, liquid chromatography with tandem mass spectrometry, chromatin immunoprecipitation sequencing RNA immunoprecipitation sequencing, *in vitro*/*in vivo* functional validation	Gemcitabine	Yes, n=45	(118)
Chabu *et al*, 2026	Pancreatic ductal adenocarcinoma	iSTORM delivers CMTM6-targeting shRNA, disrupting PD-L1 stability and inhibiting myeloid-mediated immunosuppression, thereby enhancing $CD8^+$ T-cell activation and antitumor function	*In vitro* experiments and multiple mouse models	Tumor-targeting microbial immunotherapy	No	(119)
Meng *et al*, 2022	GBM	CMTM6 enhances GBM cell migration through EMT regulation; PL markedly inhibits GBM cell proliferation and induces CMTM6	*In vitro*/*in vivo* functional validation, RT-qPCR, western blotting, flow cytometry	PL	No	(120)
Tulchiner *et al*, 2021	Renal cell carcinoma	Higher CMTM6 expression in immune cells vs. tumor cells, and it is positively associated with PD-L1	IHC	Nivolumab	Yes, n=16	(121)

Table II. Continued.

First author/s, year	Cancer type	Mechanism	Methods	Drugs	Clinical trials	(Refs.)
Wang *et al*, 2025	Breast cancer	Knockout of circUBR5 induces an 8-fold increase in miR-340-5p expression, whereas miR-340-5p directly targets and regulates CMTM6	Western blotting, flow cytometry, RNA-FISH, *in vitro*/*in vivo* functional validation	Docetaxel	No	(122)

Co-IP, co-immunoprecipitation; CMTM6, chemokine-like factor-like MARVEL transmembrane domain-containing protein 6; ENO-1, enolase-1; FISH, fluorescence *in situ* hybridization; GBM, glioblastoma; GSK3β, glycogen synthase kinase-3β; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IHC, immunohistochemistry; miR, microRNA; shRNA, short hairpin RNA; PD-L1, programmed death ligand 1; PL, piperlonguminine; RT-qPCR, reverse transcription-quantitative PCR; shRNA, short hairpin.

challenge is tumor heterogeneity: CMTM6 exhibits highly spatiotemporally dynamic expression across different cancer types, diverse microenvironmental cell populations, and under therapeutic pressure, rendering uniform strategies ineffective. The third is functional complexity: CMTM6 can drive chemotherapy resistance, stabilize EGFR signaling and reshape the immunosuppressive microenvironment via exosomes, all independently of PD-L1. In response to these challenges, current strategies are transitioning from global suppression to precision modulation. This includes the development of novel antibodies, mesoscopic chimeric peptides and nanobodies that disrupt the PD-L1-CMTM6 interaction to achieve substrate-selective intervention. Additionally, combining these strategies with immune checkpoint blockade addresses CD58 downregulation (10,125,126). The utilization of exosomal CMTM6 also facilitates non-invasive patient stratification. Collectively, these efforts aim to advance CMTM6-targeted therapy towards precision and personalized medicine.

5. Conclusions and future perspectives

The present comprehensive review systematically assessed the biological characteristics of CMTM6, its involvement in key signaling pathways, and its expression patterns and functional roles across diverse diseases. As a crucial transmembrane protein, CMTM6 serves a central role in fundamental biological processes such as cell proliferation, immune regulation and signal transduction. Aberrant CMTM6 expression has been identified in numerous types of cancer, including lung, colorectal and breast cancer, where it is associated with tumor aggressiveness, patient prognosis and therapeutic response. Beyond oncology, altered CMTM6 expression is increasingly recognized in non-neoplastic conditions, including autoimmune and chronic inflammatory diseases, suggesting its involvement in their pathogenesis and progression.

In the field of oncological therapeutics, CMTM6 has emerged as a potential therapeutic target, with its roles in immunotherapy, targeted therapy and combination treatment strategies being progressively elucidated. However, its clinical translation has numerous challenges: The broad physiological expression of CMTM6, its multi-substrate regulatory spectrum and species-specific differences constitute core safety concerns and off-target effect risks; the expression heterogeneity across tumor types, cell populations and during the course of treatment necessitates precisely stratified therapeutic strategies; and its multidimensional tumor-promoting functions independent of PD-L1, including driving chemotherapy resistance, stabilizing EGFR and remodeling the immunosuppressive microenvironment, not only add to the complexity of intervention but also provide a rationale for combination therapy.

The current research focus is transitioning from the question of whether to target CMTM6 to how to effectively target it. Strategies such as the novel antibody H1A, the mesoscopic chimeric peptide PEP-PDL1 and anti-CMTM6 nanobodies exemplify a paradigm shift from broad suppression to precision modulation. Future research should prioritize the following directions: i) Employing structural biology approaches to resolve the key structural domains mediating CMTM6 interactions with its numerous substrates, thereby providing a structural basis for the development of highly specific

inhibitors; ii) establishing preclinical evaluation systems based on humanized models, particularly utilizing humanized PD-1/PD-L1 mouse models to bridge the gap arising from species-specific differences; iii) developing liquid biopsy biomarkers such as exosomal CMTM6 for patient stratification and therapeutic efficacy monitoring; and iv) exploring optimal combination regimens integrating CMTM6-targeted therapy with existing immune checkpoint inhibitors, chemotherapy and targeted therapy, and validating their safety and efficacy in rigorously designed clinical trials. Through these systematic endeavors, CMTM6-targeted therapy is poised to advance from proof of concept to clinical benefit.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

RH was responsible for conceptualization, writing, reviewing and editing, and project administration. DM, HH, MZ and WY conducted the literature search and contributed to the writing and editing of the manuscript. BC proposed the research design, supervised the study and critically revised the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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