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REVIEW

CMTM Family and Gastrointestinal Tract Cancers: A Comprehensive Review

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Abstract: Gastrointestinal tract cancers are a highly heterogeneous group of malignant diseases, contributing significantly to the burden of death worldwide. Chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing family (CMTMs) plays important roles in cancer development and progression. Since the first member was cloned, there have been abundant studies on the relationships between the CMTM family and human cancers. It has been reported that the CMTM family has a large potential prognostic value for multiple cancers. Meanwhile, upregulated or downregulated expression of the family members was related to advanced tumor stage, metastasis, and overall survival. Studies have also reported that these proteins play critical roles in antitumor immunity. We performed a systematic review to sum up the latest advances of CMTM family' roles in gastrointestinal tract cancers, with a primary focus on hepatocellular carcinoma and gastric carcinoma.

Keywords: CMTM family, gastrointestinal tract cancers, MARVEL, hepatocellular carcinoma, gastric carcinoma

Introduction

Gastrointestinal tract cancers are a highly heterogeneous group of malignant diseases, including esophageal carcinoma (EC), gastric carcinoma (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), and pancreatic cancer (PC). These cancers contribute significantly to the burden of death worldwide, especially for CRC, with more than 1.9 million new cases estimated in the Global Cancer (GLOBOCAN) 2020 statistics and ranking third for incidence and second for mortality globally.[1] Each gastrointestinal tract tumor has distinct biological characteristics, such as cellular proliferation, disruption of cell metabolism, invasion, metastasis, promotion of angiogenesis, unique follow-up therapy, and prognosis. Although the pathogenesis of these cancers has been extensively studied, much remains unclear and further studies related to cancer-associated molecules are needed.

The chemokine-like factor super family (CKLFSF) consists of nine members: CKLF and CKLFSF 1–8, and their encoding proteins are structurally similar to chemokines.[2] CKLF1 was first cloned from a leukemia cell line stimulated by phytohemagglutinin (PHA) and reported by the Human Disease Gene Research Center of Peking University in 2001.[3] Subsequently, CKLFSF 1–8 were demonstrated through analysis combining CKLF2 cDNA and protein sequence analysis with experimental verification in 2003. Owing to the presence of a MARVEL (MAL and related proteins for vesical trafficking and membrane link) domain, CKLFSF1-8 was renamed CKLF-like MARVEL transmembrane domain containing 1–8 (CMTM1-8).

Since the first member was cloned, there have been abundant studies on the relationships between the CMTM family of proteins and human cancers. It has been reported that the CMTM family has a large potential prognostic value for multiple cancers owing to its differential expression between tumor and normal tissues.[4–8] Meanwhile, upregulated or downregulated expression of these family proteins was related to advanced tumor stage, tumor grade, metastasis, and overall survival. Studies have also reported that these proteins play critical roles in antitumor immunity.[9,10] For example, CMTM4/6 reduces

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PD-L1 ubiquitination, increases protein half-life, and enhances the ability of PD-L1-expressing tumor cells to inhibit T cells. These findings indicate that some CMTM family members are potential therapeutic targets for the treatment of human cancer. Owing to the diverse structure and function of CMTM family members and obvious heterogeneity of different human cancers, CMTM1-8 has distinct effects on malignant tumors, oncogenes, and tumor suppressors. This review briefly outlines the structure and function of CMTM1-8 in human cancers and details the latest advances in the field regarding its roles in carcinogenesis and its potential clinical value, with a primary focus on gastrointestinal tract cancers.

Characteristics of CMTM Family

CMTM members are located on different chromosomes: CMTM1-4 cluster on 16q22.1, CMTM5 cluster on 14q11.2, and CMTM6-8 cluster on 3p22.3.[2] The CMTM family is structurally and functionally characterized, similar to classic chemokines and transmembrane-4 superfamily (TM4SF). Among these, CMTM1 contains a C-C motif and shows higher sequence identity with chemokines, while CMTM8 has 39.3% amino acid similarity with TM4SF11,[2] and the biological characteristics of CMTM2-7 are between those of chemokines and TM4SF.[2,11–13] As a recently discovered gene family, the transcription of CMTM members and their quaternary structures has not been identified. Individual CMTM family members have different alternative RNA splicing forms and further make up several isoforms. We summarized the MARVEL domain of each CMTM1-8 in Figure 1 based on the AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/) and GeneCards, the human gene database (https://www.genecards.org/).

CMTM1-8 each has a MARVEL domain, a conserved M-shaped topology: four transmembrane-helix region architectures with cytoplasmic N- and C-terminal regions (Figure 1). Thus, their functional production could be related to the cholesterol-rich membrane apposition events in various biological processes, such as the biogenesis of vesicular transport carriers or tight junction regulation.[13] As MARVEL was initially identified in proteins of the myelin and lymphocyte (MAL), physins, gyrins, and occludin families, the MARVEL domain seems to be related to complex diseases, such as inflammation and schizophrenia.[13] To date, CMTM1, 2, 3, and 4 are highly expressed in the testis and compartments of the bone marrow and peripheral blood cells, such as activated peripheral blood monocytes,[14–16] while CMTM3, 5, 7, and 8 are broadly expressed in healthy adult and fetal tissues.[8,17] Therefore, CMTM1-8 appears to be involved in various human diseases, including atopic dermatitis,[18] autoimmune,[11] cerebral ischemia,[19–22] peripheral neuropathy,[23] cardiovascular diseases,[24] and spermatogenesis dysfunction.[16,25] We reviewed the relevant literature, and the research advances on the CMTM family and human cancers are summarized in Table 1.

Several biological processes, such as DNA methylation and microRNAs, as well as transcriptional regulation molecules, such as NF-κB, p53, and SOX10, regulate the expression of CMTM family members.[26,27] DNA methylation is another important regulator of CMTM family member expression. For example, CpG methylation can inactivate the CMTM5 gene in various carcinoma cell lines, such as oral squamous cell carcinoma,[28] breast carcinoma,[29] and myeloid leukemia.[30] Frequent CMTM7 promoter methylation was detected in ESCC and NPC cell lines with downregulated or silenced CMTM7, but not in other tumor cell lines. Most notably, methylation was not detected in several cancer cell lines (including KYSE180), in which CMTM7 was barely observable. This suggests that other genetic alterations or histone modifications may also be responsible for the downregulation of CMTM7.[17]

In terms of transcriptional regulation molecules, the promoter sequence of CMTM7 contains numerous regions that are highly similar to the HMG-box sequence. In line with this, SOX gene family members containing a DNA-binding domain have been reported to regulate cell differentiation and tissue formation as a highly conserved transcription factor. According to the TCGA database, a positive correlation between CMTM7 and SOX10 mRNA expression levels was detected. Additionally, knockdown of SOX10 by transfection with siRNA significantly downregulated CMTM7 expression at the mRNA and protein levels in GC cell lines.[31] Thus, SOX10 may also be a potential regulator of the expression of CMTM family members. In another study, Guan et al showed that miR-10b-3p, which plays an oncogenic role, was dramatically upregulated in HCC cell lines (HepG2), and the expression of CMTM5 was significantly suppressed.[32]

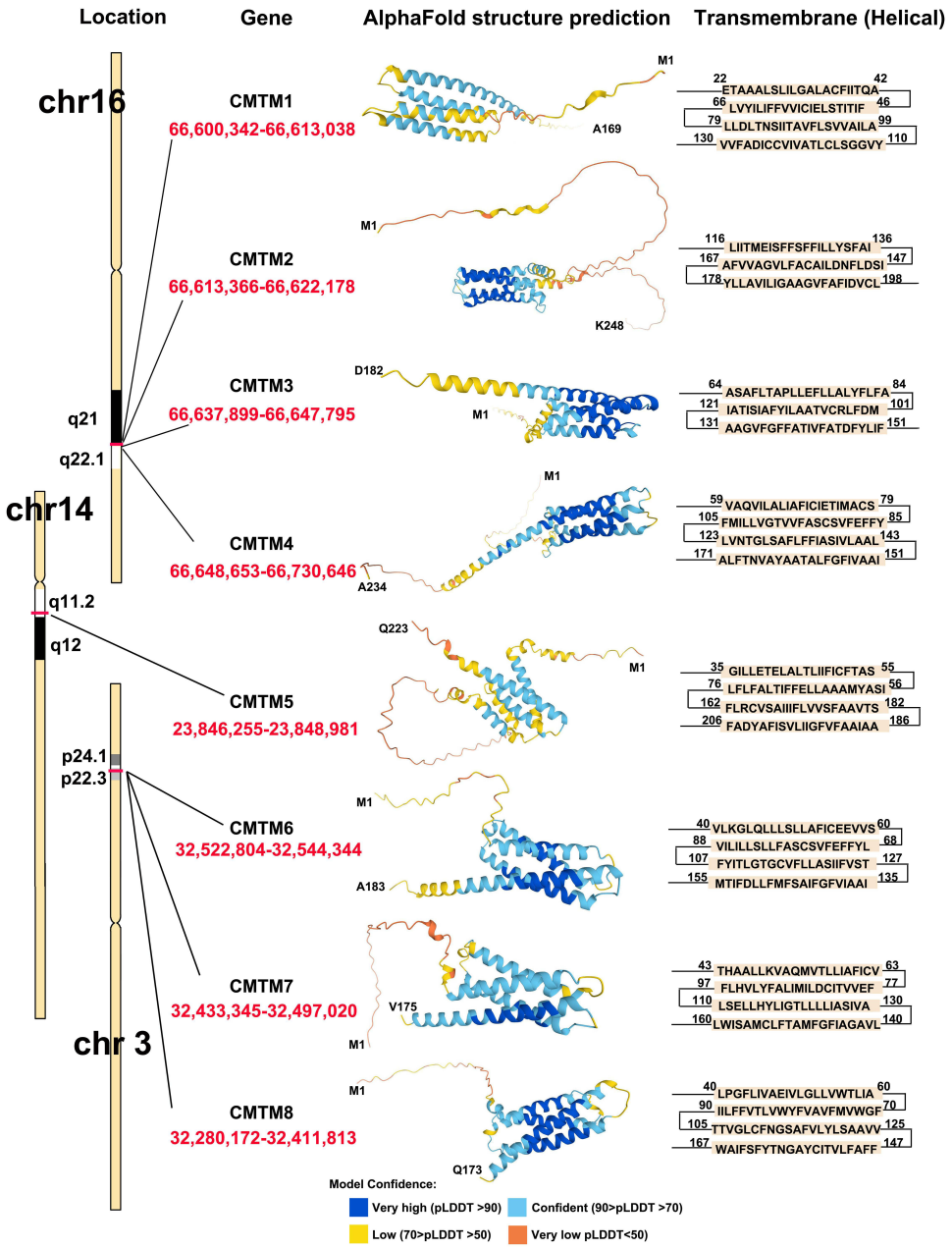

Figure 1 CMTM family members structure according to AlphaFold Protein Structure Database and GeneCards.
Notes: AlphaFold Protein Structure Database: https://alphafold.ebi.ac.uk/;[117,118] GeneCards: https://www.genecards.org/. (Structure prediction last updated on 9 December 2021).[119]

CMTM Family Members in Digestive System Cancers

Esophageal Cancer (EC)

EC is one of the most common malignant diseases, with approximately 604,000 new cases and 544,000 deaths worldwide per year.[1] Unlike other gastrointestinal tract cancers, EC has two common histologic subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which have different etiologies and geographic variations. A recent study demonstrated that the expressions of CMTM3 and CMTM4 at the mRNA and protein levels were significantly decreased in ESCC tissues compared to those in matched non-tumor tissues.[46] Meanwhile, CMTM3 expression was significantly correlated with lymph node metastasis and clinical stage in ESCC, and lower

Table 1 CMTM Family in Human Cancers

Gene	Cancer	Expression (Tumor vs Normal)	Function	Signaling Pathway	Reference
CMTM1					
	Breast carcinoma	Higher	CMTM1_v17 promotes cell proliferation	TNF-α, NF-κB	[33]
	NSCLC	Higher	Associated with chemoresistance and poor prognosis.		[6]
	HCC	Higher			[33,34]
	GC	Higher (mRNA)*	Correlated with poorer overall survival	-	[35]
	Glioblastoma	n.s.	Correlated with shorter overall survival	-	[36]
	Lymphoma	-	Induce cell apoptosis	-	[37]
CMTM2					
	HCC	Lower	Downregulated CMTM2 promotes EMT		[38,39]
	GC	n.s. (mRNA)*			[35]
	Glioblastoma	Higher (mRNA) *			[36]
CMTM3					
	HCC	Lower Higher *	Inhibits the proliferation; Regulated EMT	JAK2/STAT3	[40,41]
	GC	Lower; Higher (mRNA)*	Inhibit tumorigenicity Inhibits cell migration and invasion	EGFR; Rab5; STAT3/Twist1	[5,35,42–44]
	PC	Higher	Promotes cell proliferation and migration		[45]
	ESCC	Lower	Associated with a favorable prognosis		[46]
	Glioblastoma	Higher (mRNA)*	Correlated with shorter overall survival		[36]
	Renal cell carcinoma	Lower	Exhibits tumor suppressor activities		[51]
	Prostate cancer	Lower	Inhibits migration and invasion	Erk1/2	[52,53]
	OSCC	Lower	Inhibits cell growth and migration		[54,55]
	Chordoma	Lower	Regulated EMT and TP53, Suppresses progress	EGFR/STAT3	[56]
CMTM4					
	HCC	Lower Higher	Tumor suppressor; An important prognostic and diagnostic marker; Facilitates escape from antitumor T-cell immunity and tumor growth		[57–59]
	GC	n.s. (mRNA)*			[35]
	CRC	Lower	Inhibits cell proliferation and migration	AKT, ERK1/2, STAT3	[60]
	Clear cell renal cell carcinoma	Lower	A tumor suppressor		[61,62]
	HNSCC	Higher	Regulates EMT and PD-L1 expression	AKT	[63]
	HeLa cell		Inducing G_2/M phase accumulation		[64]
	Glioblastoma	Lower (mRNA)*	-		[36]
CMTM5					
	HCC	Lower	Suppresses tumor growth	PI3K/AKT	[65]
	Breast carcinoma	Lower*	A prognostic biomarker and potential therapeutic target		[66–68]
	Prostate cancer		Inhibits cell proliferation and migration	EGFR; HER2	[69,70]
	Renal cancer	Lower	Inhibits renal cancer cell growth through inducing cell-cycle arrest and apoptosis		[71]
	Cervical carcinoma cells	-	Induces apoptosis		[72]

(*Continued*)

Table 1 (Continued).

Gene	Cancer	Expression (Tumor vs Normal)	Function	Signaling Pathway	Reference
	OSCC	Lower	Tumor suppressor activity		[28]
	Epithelial ovarian cancer	Lower		-	[73]
	PC cells	Lower	induces apoptosis	TNF-α	[74]
	Leukemia	Lower	Tumor suppressive function		[30]
	Multiple myeloma progression	Lower	Inhibits the proliferative activity		[75,76]
CMTM6					
	HCC	Lower [55]; Higher	Related to inflammatory cell density; Promotes migration, invasion, and EMT; Stabilizing PD-L1; Associated with tumor recurrence.	B7 family, Vimentin, PD-L1	[77–81]
	GC	Higher	a useful prognostic indicator		[39,40]
	CRC	Higher	Associated with an active immune microenvironment, a favorable prognosis.		[84,85]
	NSCLC	Lower in lung adenocarcinoma	Correlated with PD-L1 expression and immune cells infiltration		[4,86–89]
	HNSCC	Higher	Promotes cell proliferation and invasion; drives cisplatin resistance; Induced M2-like macrophages polarization	Wnt/β-catenin, TGFβ; ENO-1/ AKT/GSK3β; ERK1/2	[90–94]
	Gliomas	Higher	Regulating T cell activation and antitumor and responses		[7]
	Undifferentiated pleomorphic sarcoma		Correlated with the strong expression of PD-L1		[95]
	Glioblastoma	Higher (mRNA)*	-		[36]
CMTM7					
	HCC	Lower	Inhibits cell growth and migration		[96]
	GC	Lower	Inhibits cell proliferation and tumor growth		[31]
	NSCLC		CMTM7 knockdown increases tumorigenicity, a potential tumor suppressor	EGFR-AKT, Rab5	[97,98]
CMTM8					
	HCC	Lower	Down-regulation induces EMT, regulating tumor cell migration	HGF/ c-MET/ERK	[99]
	GC	Lower(IHC) Higher (mRNA)*	Downregulated CMTM8 correlates with Poor prognosis		[100]
	Bladder cancer	Lower	Inhibits the carcinogenesis and progression		[8,101]
	PC	LPA1 and CMTM8 were co-localized	Mediates lysophosphatidic acid-induced metastasis	LPA1-associated partner	[114]
	Renal cell carcinoma	Lower			[103]
	Glioblastoma	Lower (mRNA)	-		[36]

Note: *Bioinformatics analysis.

Abbreviations: HCC, hepatocellular carcinoma; GC, gastric carcinoma; ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; CRC, colorectal cancer.

CMTM3 expression correlated with shorter survival time for ESCC patients. This indicates that the expression of CMTM3 in resected tumors may be an effective prognostic biomarker.[46] CMTM5-v1 was reported to be reduced or silenced in 12 of 16 ESCC cell lines,[29] while CMTM7 is frequently silenced or downregulated in eight of 18 ESCC cell lines (44.4%), such as EC109, KYSE410, and KYSE180.[17] Meanwhile, promoter methylation of CMTM5 and CMTM7 was also detected in esophageal tumor tissues and cell lines.[17,29] Overexpression of CMTM7 by adenovirus infection promoted the internalization of epidermal growth factor receptor (EGFR) and further downregulated p-AKT.[17] CMTM7 also inhibited cell proliferation and motility in KYSE410 and KYSE180 cells by inducing G_1/S cell cycle arrest by upregulating p27 and downregulating cyclin-dependent kinase 2 (CDK2) and 6 (CDK6). Interestingly, MAL proteins, which are essential components of the cellular polarized sorting system, have been reported to suppress cell invasion and tumorigenicity of cervical squamous cell cancers, suggesting that it may be a candidate tumor suppressor gene.[104] It is possible that CMTM3, 5, and 7 act as novel functional critical tumor-suppressor genes in ESCC.[17] At present, there are no studies on CMTM1-8 in EAC.

Gastric Carcinoma (GC)

GC remains a critical cancer worldwide and is responsible for over 1,089,103 new cases and an estimated 768,793 deaths in 2020, ranking fifth for incidence and fourth for mortality globally.[1] Although GC is generally reported as an entity, it can be divided into two topographical subsites: cardia adenocarcinoma and non-cardia adenocarcinoma. The two entities differ in their risk factors, carcinogenesis, and epidemiologic patterns.[47–50] Recently, an analysis using bioinformatics methods showed that the mRNA levels of CMTM1, 3, 6, 7, and 8 were upregulated in GC, but CMTM2, 4, and 5 were not significantly different between GC samples and normal tissue. Additionally, the mRNA expression of CMTM family members exhibited strong relationships with various clinical characteristics of patients, such as tumor stage, metastatic lymph node status, and *H. pylori* status. For example, elevated CMTM3 and 5 mRNA levels were significantly associated with poor overall survival, while upregulated mRNA expression of CMTM2, 4, and 6 was significantly associated with better overall survival. These results indicate that the CMTM family expression pattern could be a novel prognostic factor for patients with GC.[35]

In contrast, CMTM3 was reported as a tumor suppressor gene in GC patients with different tumor stages using immunohistochemistry (IHC). High expression of CMTM3 might correlate with favorable prognosis of patients, and CMTM3 expression significantly affected the migration and invasion of gastric cell lines (AGS and SGC-7901 cells). CMTM3 not only inhibited EGF-mediated tumorigenicity by inducing Rab5 activity, but also suppressed GC metastasis via the STAT3/Twist1/EMT pathway.[5,42,43] Meanwhile, patients with diffuse-type GC and higher CMTM2 expression had a better overall survival, indicating that CMTM2 expression could predict the prognostic outcomes in diffuse-type GC, but not in intestinal-type GC.[105] CMTM5-v1 was reduced or silenced in eight of 10 GC cell lines.[29]

CMTM6, 7, and 8 are broadly expressed in normal human epithelial cell lines. A recent study showed that GC patients with high CMTM6 expression had shorter overall survival (OS),[82] and the co-expression of CMTM6 and PD-L1 may be used to judge the prognosis of GC patients.[83] Although only one of 16 GC lines (6.25%) showed CMTM7 downregulated expression, the downregulation of CMTM7 was detected in GC tissues using tissue microarrays.[17] Interestingly, silencing CMTM7 expression could increase the proliferation and promote tumorigenesis of GC cells, while the overexpression of SOX10-dependent CMTM7 significantly inhibited the tumor growth of GC.[31] Contrary to the bioinformatics results of the Oncomine database,[35] IHC results showed that the positive rate of CMTM8 protein expression was significantly decreased in GC samples compared to that in adjacent non-tumor tissues, and its expression was correlated with tumor differentiation and node metastasis stage.[100] The reason for this discrepancy may be that there are some differences between mRNA and protein expression of CMTM8 regarding posttranscriptional regulation. CMTM8 overexpression significantly decreased the proliferation of the gastric cell line BGC823 and the expression of EGFR.[43] In addition, multiple gene set enrichment analyses (GSEA) showed that CMTM8 could regulate the Ca^{2+} signaling pathway, cell adhesion molecules, and interaction of cytokines and their receptors in GC progression.[106] Therefore, CMTM3, 7, and 8 tend to be regarded as tumor suppressors in the development of GC.

Hepatocellular Carcinoma (HCC)

Primary HCC is the sixth most commonly diagnosed malignancy and the third leading cause of cancer-related deaths worldwide, with 905,677 new cases and 830,180 deaths in 2020.[1] The liver, one of the most common hematogenous metastasis organs of gastrointestinal malignancies, has attracted more interest from the community and research on CMTMs. Recent studies have revealed that CMTMs are closely related to HCC, and the members might represent promising targets for HCC diagnosis and treatment. Based on the Human Protein Atlas and bioinformatics analysis, a higher level of CMTM1 mRNA expression was associated with a lower survival probability in patients with HCC.[34] Although CMTM2 is not a prognostic index in HCC according to data from the Human Protein Atlas, several studies have revealed that CMTM2 expression is correlated with HCC pathological grades.[38] In addition, knockdown of CMTM2 promoted invasion and migration of HCC cells (Huh-7 and SMMC7721) by inducing the epithelial-mesenchymal transition (EMT) process.[39] The Human Protein Atlas showed that CMTM3 expression was higher in liver tumor tissues and was associated with poor prognosis.[34] However, Li et al reported that the expression of CMTM3 was lower in HCC cell lines (HepG2, 97H, Hep3B, and HCCLM3), and CMTM3 inhibited the proliferation and metastasis of HCC cells by suppressing the JAK2/STAT3 signaling pathway.[40] Moreover, Zhao et al suggested that CMTM3 may participate in regulating the tumor microenvironment in an orthotopic HCC mouse model.[107]

A case-control study in the southern Chinese population showed a strong correlation between rs3811178 in CMTM5 and the risk of HCC.[108] Compared with the paired adjacent non-tumor tissues, CMTM5 was significantly reduced in HCC tissues, as well as in Huh7, Hep3B, HepG2, and SMMC-7721 cell lines. CMTM5 overexpression significantly inhibited cell proliferation and metastasis in Huh7 cells by inhibiting PI3K/AKT signaling.[65] In addition, a previous study demonstrated that CMTM5 expression could be restored in HCC treated with PXD101, a histone deacetylase inhibitor.[109] Thus, CMTM5 may be a valuable therapeutic target for HCC treatment.

As for the CMTM4 expression in HCC, there are two inconsistent opinions. One study reported a lower CMTM4 protein expression level in HCC tissues,[57] while another two studies showed upregulation of CMTM4 at the mRNA and protein levels.[58,59] Furthermore, the upregulated CMTM4 expression in HCC facilitates escaping from antitumor T-cell immunity and contributes to an immunosuppressive tumor microenvironment.[59] Similar to CMTM4, CMTM6 expression was downregulated[78] or upregulated[80,110] in HCC tissues. The reasons for the contradiction between these studies are still ambiguous; however, small-scale specimens, heterogeneity of tumor tissue, and observational bias are possible factors. Interestingly, immunoreactive cellular distribution showed positive CMTM6 expression in all proliferative lesions from the early stage in the piperonyl butoxide (PBO)-induced hepatocarcinogenesis mouse model.[111] Meanwhile, CMTM6 had a high concordance ratio with CK8/18+ foci, a useful immunohistochemical marker for detecting hepatocellular proliferative lesions in mice.[112] Individuals from Guangxi, China, with the rs164207 AA genotype of CMTM6, have a higher risk of HCC than those with the CC genotype.[108] These results suggest that CMTM6 may play important roles in the early stages of carcinogenesis and could be used as a detection marker for hepatocellular proliferative lesions.[111]

Recent studies have shown that CMTM6 expression is upregulated in HCC tissues, and its overexpression increases cell proliferation and enhances cell invasion and migration and induces epithelial–mesenchymal transition (EMT) mechanistically by stabilizing vimentin.[80] In addition, the co-expression of CMTM6/PD-L1 can regulate inflammatory cell density[77] and has a close relationship with tumor recurrence.[81] Given the participation of CMTM6 in PD-L1 stabilization,[9,10] combined treatment with anti-CMTM6 and anti-PD-L1 may be a new method to enhance the therapeutic benefits in HCC.

The expression of CMTM7 was significantly reduced in liver cancer tissues, but was not correlated with TNM stage or metastasis. Overexpression of CMTM7 inhibited the proliferation and migration of HCC cell lines (SK-HEP-1). Thus, CMTM7 functions as a tumor suppressor in liver cancer by suppressing cell cycle progression.[96]

Pancreatic Cancer (PC)

PC is generally regarded as one of the most lethal malignancies, with a median overall survival of 6 months and a 5-year survival rate of less than 5%.[102] The 2020 GLOBOCAN statistics showed that in 185 countries pancreatic cancer accounts for almost as many deaths (466,003) as cases (495,773) due to its poor prognosis.[1] Using a pancreatic cancer tissue microarray, CMTM5 was significantly decreased in pancreatic cancer tissues and

was directly correlated with the differentiation status of tumors.[74] Restoration of CMTM5-v1 not only induced apoptosis of pancreatic cancer cells (MIA PaCa-2), but also had synergistic effects with TNF-A.[74] Pancreatic stellate cell (PSC)-derived exosomes, miR-5703, promoted cell proliferation, and its inhibitor suppressed the function of exosomes. Furthermore, CMTM4 was downregulated by miR-5703 directly bound to the CMTM4 3′UTR, and CMTM4 knockdown promoted cell proliferation owing to the PAK4-activated PI3K/AKT pathway in pancreatic cancer cells.[113] A recent publication reported that CMTM8 protein was co-localized with lysophosphatidic acid (LPA)-1 in pancreatic cancer cells and markedly increased after LPA treatment. However, CMTM8 mRNA abundance showed no significant change in BxPC-3 and PANC-1 cells treated with LPA, implying that LPA treatment stabilizes CMTM8 protein. Meanwhile, depletion of CMTM8 knockdown significantly inhibited the migration and invasion of pancreatic cancer cells in vivo.[114] To date, with the exception of CMTM4, 5, and 8, no reports on the role of the other CMTM family members in pancreatic cancer are available. Further studies are needed to elucidate the underlying mechanisms of CMTMs in the development of pancreatic cancer.

Colorectal Cancer (CRC)

CRC ranks third in terms of incidence, but second in terms of mortality worldwide. In 2020, more than 1.9 million new CRCs were estimated to occur.[1] However, after a large number of studies were reviewed, only a few studies have focused on the roles of CMTMs in CRC. CMTM3 is silenced or downregulated in colon cell lines and primary tumors, consistent with the results from the Cancer Genome Atlas (TCGA) database,[44,115] while re-expression of CMTM3 can inhibit cell growth and cause apoptosis in human cancer cells.[44,116] Xue et al found that CMTM4 was also frequently reduced in CRC, and CMTM4 overexpression was associated with increased overall survival rates. Overexpression of CMTM4 inhibited cell proliferation and migration in SW480 cells, and knockdown of CMTM4 showed the opposite effects in HT-29 cells.[60] The phosphorylation levels of cell signaling molecules essential for CRC progression, including AKT, ERK1/2, and STAT3, were decreased by CMTM4 overexpression in SW480 cells and increased by CMTM4 knockdown in HT-29 cells.[60] CMTM7 was methylated in primary esophageal carcinomas and GC, but not in any of the 11 colon tumor tissues.[17] Since a protective role for PD-L1 was reported in Nature, the latest research has shown that CMTM6 is crucial in regulating the immune microenvironment in CRC, and the co-expression of CMTM6 and PD-L1 can be used to stratify the risk of progression in CRC patients.[75] Meanwhile, the expression status of CMTM6 in M2 macrophages may more accurately predict the drug response to PD-1/PD-L1 inhibitors in CRC patients.[85] To date, the roles of other CMTM members in CRC, except for CMTM3, 4, and 6, are largely unknown.

Conclusion

To summarize, CMTM family members have different expression profiles in human cancer samples and normal tissues and have different functions in the development and progression of gastrointestinal tract cancers. Meanwhile, they were reported to be tumor suppressors or tumor promoters owing to their relationships with the regulation of the cell cycle, EMT process, and EGFR signaling pathway (Table 2). The heterogeneity of different tumors and distinct molecular structures of each CMTM member make this family in human cancers controversial. With the exception of CMTM4/6, demonstrated to be PD-L1 regulators and may be potential immunotherapy targets, the mechanism of the other members remains partially understood. Hence, the CMTM family and their functions, mechanisms, and related signaling pathways in gastrointestinal tract cancers need to be further explored as these could provide a new viewpoint for the diagnosis or therapeutic targets of human cancers.

Statements and Declarations

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Table 2 The Roles of CMTM Family in Gastrointestinal Tract Cancers

Gene	Roles (Promoter/Suppressor)				
	EC	HCC	GC	PC	CRC
CMTM1	NA	NA	Promoter	NA	NA
CMTM2	NA	Suppressor	NA	NA	NA
CMTM3	Suppressor	Suppressor	Suppressor	Suppressor	NA
CMTM4	NA	Promoter/suppressor	NA	Promoter	Suppressor
CMTM5	NA	Suppressor	NA	Suppressor	NA
CMTM6	NA	Promoter/suppressor	NA	NA	NA
CMTM7	Suppressor	Suppressor	NA	NA	NA
CMTM8	NA	Suppressor	Suppressor	Promoter	NA

Disclosure

The authors declare no conflicts of interest in this work.

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