

Chemokine-like factor-like MARVEL transmembrane domain-containing family in autoimmune diseases

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Abstract

The chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing family (CMTM) is widely expressed in the immune system. Abnormal expression of CMTM is associated with the development of various diseases. This article summarizes the relevant research on the role of the CMTM family in immune disorders. This information will increase our understanding of pathogenesis and identify promising targets for the diagnosis and treatment of autoimmune diseases. The CMTM family is highly expressed in peripheral blood mononuclear cells. CKLF1 may be involved in the development of arthritis through its interaction with C-C chemokine receptor 4. CKLF1 is associated with the pathogenesis of lupus nephritis and psoriasis. Both CMTM4 and CMTM5 are associated with the pathogenesis of systemic lupus erythematosus. CMTM1, CMTM2, CMTM3, and CMTM6 play a role in rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, and anti-phospholipid syndrome, respectively. The CMTM family has been implicated in various autoimmune diseases. Further research on the mechanism of the action of CMTM family members may lead to the development of new treatment strategies for autoimmune diseases.

Keywords: CMTM; CKLFSF; Autoimmune Diseases; Immune system

Introduction

The chemokine-like factor super family (CKLFSF), a new class of chemokines, was discovered by Peking University Human Disease Gene Research Center. CKLF1, which was isolated from phytohemagglutinin (PHA)-stimulated U937 cells, was the initial member of the CKLFSF.^[1] Subsequent studies identified CKLFSF1-8 using a combination of bioinformatics and reverse transcription polymerase chain reaction techniques. The CKLFSF consists of nine genes, CKLF and CKLFSF1-8.^[2,3] The characteristics of their gene products lie somewhere between classical chemokines and members of the transmembrane 4 super family (TM4SF).^[2] According to their structural features, the Human Gene Nomenclature Committee recommended denominating CKLFSF1-8 as CKLF-like MARVEL transmembrane (CMTM)1-8 [Figure 1].^[4] The CMTM family members are widely expressed throughout the immune system and they are associated with autoimmune diseases.^[2] Therefore, CMTM members may represent promising targets for the diagnosis and treatment in autoimmune diseases. This article summarizes the relevant research on the role of the CMTM family in the immune system and autoimmune diseases.

CMTM Family Members and the Immune System

CKLF1

CKLF1 is located on chromosome 16q 22.1 and has four exons and three introns. There are at least three alternative RNA splicing forms: CKLF2, CKLF3, and CKLF4. The expression of CKLFs in tissues is variable. CKLF1 expression is similar to that of CKLF2, but higher than that of CKLF4. CKLF3 expression is comparatively the lowest. CKLF1 and CKLF3 are secreted proteins, while CKLF2 and CKLF4 are transmembrane proteins. CKLF2 and CKLF4 are primarily located on the cell periphery.^[1]

CKLF1 is different from classical chemokines. CKLF1 has a CC motif, but lacks the additional C-terminal cysteines as compared with the other classical CC sub-family members.^[1] However, the key amino acids surrounding the CKLF1 motif are similar to those of thymus- and activation-regulated chemokine (TARC)/C-C class chemokines (CCL) 17 and macrophage-derived chemokine (MDC)/CCL22.^[2] Previous studies have shown that both TARC/CCL17 and MDC/CCL22 are specific ligands for C-C chemokine receptor 4 (CCR4).^[5,6] Several *in vitro* experiments found that CKLF1 induced calcium flux in CCR4-transfected HEK293 cells and desensitized CCR4

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Website:
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DOI:
10.1097/CM9.0000000000000747

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Chinese Medical Journal 2020;133(8)

Received: 31-10-2019 Edited by: Li-Shao Guo

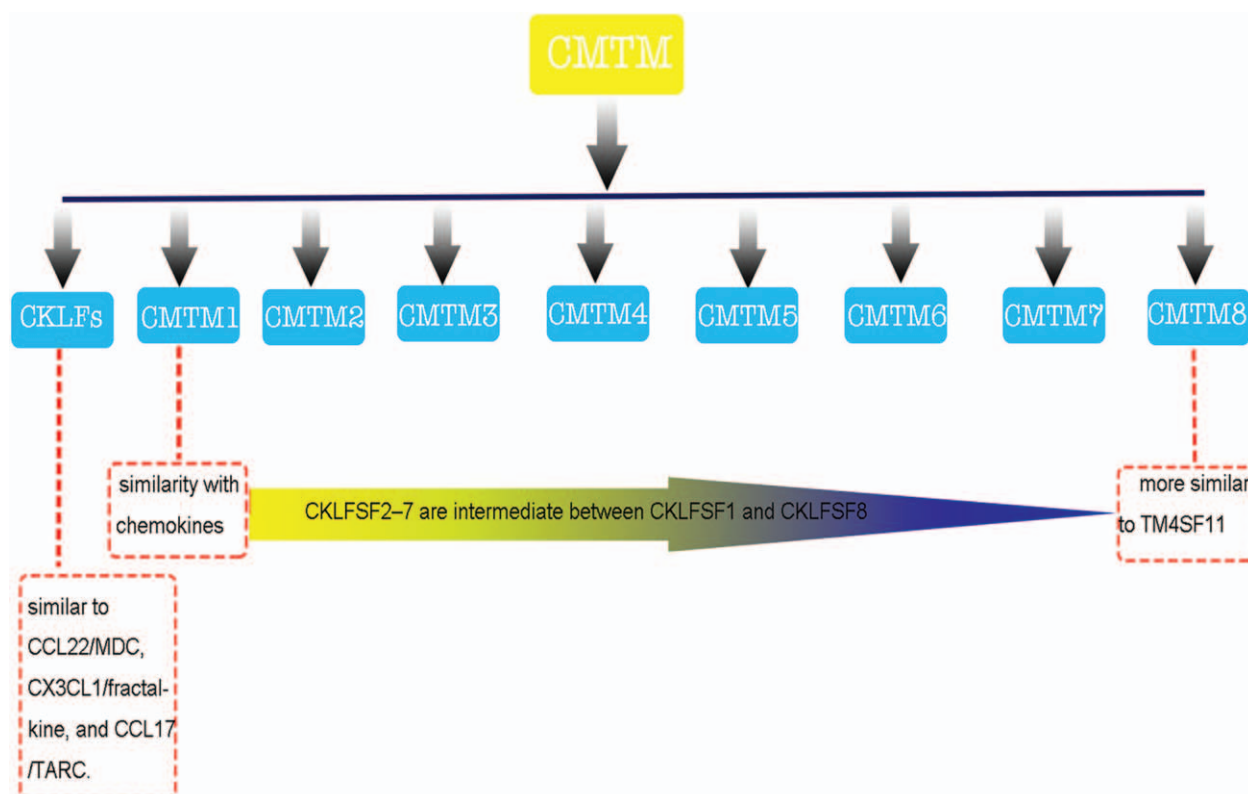


Figure 1: The composition of the CMTM family. The characteristics of CMTM members lie between that of classical chemokines and transmembrane 4 super family (TM4SF) members. CCL: C-C class chemokines; CMTM: Chemokine-like factor (CKLF)-like MARVEL transmembrane; CX3CL: CX3C chemokine ligand; MDC: Macrophage-derived chemokine; TARC: Thymus-and activation-regulated chemokine.

transfectants to subsequent TARC/CCL17 treatment. Meanwhile, the internalization of CCR4 receptors was significantly increased following treatment with CKLF1 in pCCR4-enhanced green fluorescent protein transfected cells.^[7] CKLF1 is a novel functional ligand for CCR4.^[8] CCR4 is a chemokine receptor that has been shown to promote recruitment, homing, and education of activated leukocytes (mainly CD4⁺ Th2 lymphocytes).^[6,9] Moreover, CCR4 is expressed on dendritic cells (DCs), basophils, T cells, and platelets.^[10] This suggests that the interaction of CKLF1 with CCR4 might play a role in autoimmune diseases.

CKLF1 has a broad spectrum of chemotactic activity for many cells including lymphocytes, macrophages, and neutrophils.^[11] Li *et al*^[12] reported that CKLF1 expression was increased in activated CD4⁺ and CD8⁺ lymphocytes. They further explored the kinetic expression of CKLF1 in PHA-stimulated (specific for T lymphocytes) peripheral blood lymphocytes and found that CKLF1 was significantly increased in a time-dependent manner. This was similar to the expression of CD25 (an activation marker of T cells).^[12,13] These studies suggest that CKLF1 could be involved in T lymphocyte activation.^[14] Previous studies have shown that CKLF may exhibit chemotactic activity and activate neutrophils through mitogen-activated protein kinase (MAPK) pathway. Anti-CKLF1 antibody decreased the production of the inflammatory factors tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , macrophage inflammatory protein-2 and IL-8 as well as

the adhesion molecules, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1.^[15] In addition, CKLF1 was found to be highly expressed in monocytes. Shao *et al*^[16] reported that, during DCs differentiation, CKLF1 was increased on day 2 and decreased on days 3 to 5. The expression of CKLF1 in DCs activated by stimuli was demonstrated to be lower compared with immature DCs.^[16] DC maturation requires the activation of nuclear factor (NF)- κ B transcription.^[17] In a recent study, researchers demonstrated that IMM-H004 (a novel coumarin derivative screened from a CKLF1/C-C CCR4 system) protects against ischemic stroke-induced inflammation through a CKLF1 pathway in coordination with NF- κ B.^[18-20] Thus, the function of CKLF1 in DC maturation may involve the NF- κ B pathway.^[16] Furthermore, GC-Th cells were shown to significantly up-regulate the expression of C-X-C motif chemokine ligand (CXCL) 13, CKLF1 and inducible co-stimulator, which are important costimulatory molecules in the humoral immune response and germinal center formation.^[21]

CKLF1 has two secreted forms at the C-terminus, known as C19 and C27.^[22] The C19 peptide lacks eight amino acids at its N-terminus compared with the C27 peptide. This truncated region is important for receptor chemotaxis, calcium flux, and heparin binding.^[23] Both C19 and C27 can interact with CCR4, whereas C27 exhibits more activity than C19. C27 acts as an agonist of CCR4, whereas C19 acts as an antagonist.^[22] Furthermore, C19 and C27 inhibit stromal cell-derived factor-1 (SDF-1)-induced

C-X-C motif chemokine receptor (CXCR) 4-mediated chemotaxis by binding to CCR4 and activating phosphatidylinositol 3-kinase /protein kinase C pathway-mediated cross desensitization.^[24] Both C19 and C27 may increase the capacity of immature DCs to induce proliferation and interferon (IFN)- γ production by T cells. C19 and C27 also up-regulate the expression of HLA-DR and the production of IL-12 in immature DCs.^[25] Zheng *et al*^[26] reported that intranasal treatment with large doses of C19 significantly reduced the numbers of Th2 cells. Finally, the expression of CKLF1 is up-regulated in various autoimmune diseases.^[27]

CMTM1–5

CMTM1–4 is located in a gene cluster on chromosome 16q22.1.^[28] *CMTM1* consists of seven exons, six introns, and consists of 23 isoforms that are highly expressed in testis and tumor tissues. *CMTM1* may play a role in spermatogenesis or testicular development and tumorigenesis.^[29,30] *CMTM2* is tightly linked with *CMTM1*, which is also highly expressed in testis, located in spermatogonia and secreted into the seminiferous tubules. Meanwhile, *CMTM2* is expressed in bone marrow and peripheral cells, including CD4⁺T cells.^[31] Intra-cellular *CMTM2* can negatively regulate HIV-1 transcription in Jurkat (lymphoblastoid T-cell line) and U937 (human monocyte cell line) cells by targeting the AP-1 and cyclic adenosine monophosphate (AMP) response element binding (CREB) signaling pathways. *CMTM2* may have unknown immune related functions.^[32]

CMTM3 is highly expressed in the immune system and the male reproductive system.^[4] Previous study reported that *CMTM3* was highly expressed in peripheral blood mononuclear cells (PBMCs).^[2] In a cDNA library prepared from peripheral blood, *CMTM3* was predominantly expressed in resting B lymphocytes. *CMTM3* is also highly expressed in CD4⁺ T lymphocytes and monocytes. These studies suggest that *CMTM3* has a significant function in the immune system.^[4] Moreover, *CMTM3* can be released via exosomes.^[33] *CMTM4* has three transcript variants, *CMTM4-v1*, *CMTM4-v2* and *CMTM4-v3*. *CMTM4* is a regulator of the programmed cell death-ligand 1 (PD-L1) protein.^[34]

CMTM5 is located on chromosome 14q11.2.^[35] While studying granulopoietic gene expression, Liu *et al*^[36] found that *CMTM5* was expressed in the granulocyte system and is up-regulated during the process of differentiation. *CMTM5* may have immune related functions. *CMTM5-v1* is secreted via a vesicle-mediated secretory pathway.^[37]

CMTM6–8

CMTM6–8 is located in a gene cluster on chromosome 3p22. *CMTM6* is a widely expressed protein.^[38] Studies have shown that *CMTM6* regulates anti-tumor immunity by maintaining the expression of PD-L1.^[39] Interference with *CMTM6* expression resulted in impaired PD-L1 protein expression in all tested tumor cell types and primary human DCs.^[39] Murine *CMTM7* is highly expressed in immune cells.^[40] Thus, *CMTM7* may play

an important role in the immune system. *CMTM7* links B cell receptor (BCR) and B-cell linker protein (BLNK), and initiates BLNK-mediated signal transduction in B cells.^[41] Zhang *et al*^[40] demonstrated that *CMTM7* plays a specific role in BCR expression and survival of B-1a cells. A recent study reported that *Cmtm7* controls B-1a cell development at the transitional stage.^[42] Moreover, increased numbers of B-1a cells are often associated with autoimmunity.^[43] *CMTM8* is more structurally similar to TM4SF11^[2] and is a negative regulator of epidermal growth factor (EGF)-induced signaling.^[44]

CMTM Members and Autoimmune Diseases

Autoimmune diseases represent a series of diseases, ranging from organ-specific diseases (antibodies and T cells react to localized autoantigens in specific tissues) to organ-non-specific or systemic diseases (characterized by reacting to antigens distributed throughout various tissues).^[45] According to previous studies, *CMTM* members are highly expressed in the immune system.^[2] Here, we discuss the relationship between the *CMTM* and autoimmune diseases.

CKLF1

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by an autoimmune response to self-antigens which can affect organs and tissues such as the brain, blood, and kidneys.^[46,47] Lupus nephritis (LN) is a major risk factor for morbidity and mortality in SLE patients.^[48] Previous studies have suggested that the pathogenesis of LN was associated with neutrophil activation. In a model of SLE, researchers reported that the disease may initiate pre-clinically with an IFN response followed by differentiation of B cells into plasmablasts.^[49] As mentioned above, *CKLF1* was associated with neutrophil activation, IFN production, and B cell function. *CKLF1* may play a role in the pathogenesis of LN. The expression of the *CKLF* gene was found to be associated with the development of LN in a study of the molecular mechanism of renal inflammation during the progression, remission, and recurrence of LN in mice.^[50] High expression of *CKLF1* may be related to the excessive involvement of inflammatory cells in chemotaxis and *CKLF1* may mediate the immune inflammatory reaction process observed in LN [Figure 2]. In this experiment, *CMTM* was transferred into SLE mice, resulting in high expression of *CKLF1*, which increased the urine protein level in SLE mice and aggravated the inflammatory reaction.^[51] In a clinical study, the expression of *CKLF1* in lupus patients was increased and positively correlated with the lupus active index compared with healthy controls.^[52]

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which can lead to cartilage and bone damage. Early diagnosis is the key to optimal treatment.^[53] T-cell response may be involved in the pathogenesis of RA.^[54] An increase in citrulline-specific T-helper-1 cells was found in the circulation of patients with RA, especially in patients with early disease.^[55] Leukocyte infiltration into the synovial and chemokine network play a role in the

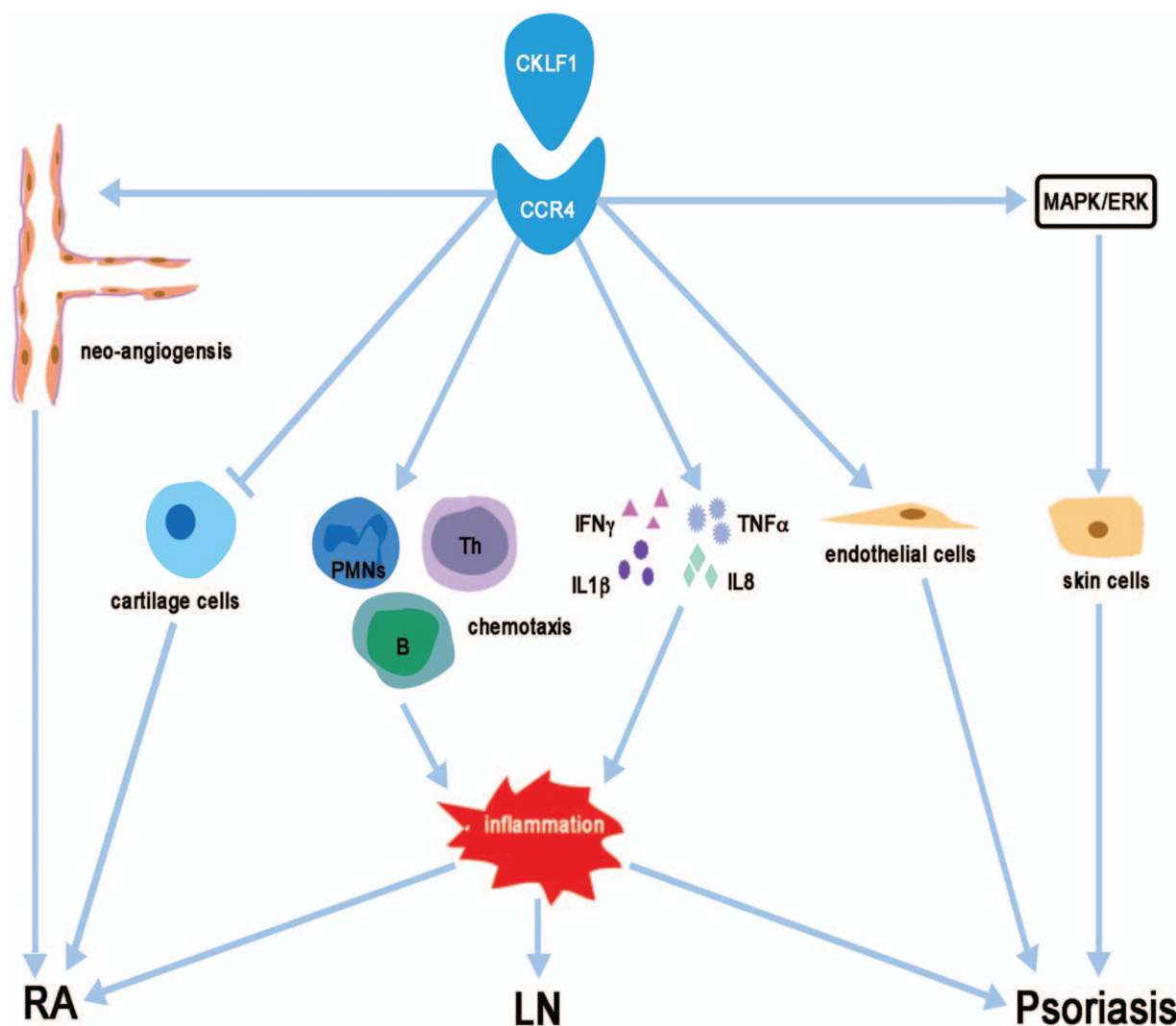


Figure 2: The major mechanisms regulated by CKLF1 in autoimmune diseases. CKLF1 may mediate the immune inflammatory reaction process in LN; CKLF1 may promote development and progression of the inflammatory response and neo-angiogenesis and inhibit cartilage cell proliferation in RA; CKLF1 may promote the proliferation of endothelial cells, participate in local inflammation and dysregulate the function of psoriatic skin cells. CCR4: C-C chemokine receptor 4; CKLF: Chemokine-like factor; ERK: Extracellular signal-regulated kinase; IFN: Interferon; IL: Interleukin; MAPK: Mitogen-activated protein kinase; PMNs: Polymorphonuclear leukocytes; LN: Lupus nephritis; Th: T helper cells; RA: Rheumatoid arthritis; TNF: Tumor necrosis factor.

pathogenesis of RA.^[56,57] Osteoarthritis (OA) is the most common joint disease that affects one or several diarthrodial joints.^[58] OA is considered to be a disease of the whole joint, including articular cartilage, subchondral bone, ligament, articular capsule, and synovium, which eventually leads to joint failure.^[59] Ankylosing spondylitis (AS) is a chronic inflammatory arthritis and the initiation of AS is unknown. T cells and TNF- α are involved in the pathogenesis of AS.^[60] Chemokines play an important role in the pathogenesis of arthritis by inhibiting the synthesis and metabolism of articular cartilage and promoting the degradation of the matrix.^[61] Rioja *et al*^[62] reported that CKLF1, as measured by microarray analysis, was up-regulated in joints in a reactivation model of SCW-induced arthritis in Lewis (LEW/N) rats. A recent study found that the expression of CKLF1 was up-regulated in synovium from AS and RA patients, and CCR4 mRNA levels were increased in RA patients, but not in OA or AS patients. Meanwhile, this study also found that the expression levels of CKLF1 were correlated with C-reactive protein/

erythrocyte sedimentation rate (ESR) and ESR in RA and AS patients, respectively.^[63] Dysregulation of NF- κ B plays an important role in the pathogenesis of arthritis.^[64] Keith *et al*^[65] reported that WAY-169916, a selective NF- κ B transcriptional inhibitor, caused a marked decrease in CKLF1 expression in rat spleens. Consequently, CKLF1 may bind to CCR4 and promote development and progression of the inflammatory response and neo-angiogenesis in rheumatic diseases [Figure 2].^[63] Furthermore, CKLF1 may inhibit cartilage cell proliferation, collagen, and protein polysaccharide synthesis.^[66] Thus, CKLF1 may play an important role in the pathogenesis of arthritis.

Psoriasis is an immune-mediated genetic disease characterized by hyperproliferation of the epidermis, accumulation of inflammatory cells, and dilation of dermal papillary vessels.^[67] CKLF1 is associated with the pathogenesis of psoriasis. A recent study has shown that CKLF1 and CCR4 are highly expressed in psoriatic lesions. CKLF1 may

promote the proliferation of microvascular endothelial cells and contribute to local inflammation. It has been demonstrated that the MAPK/extracellular signal-regulated kinase (ERK) signaling pathway plays an important role in the pathophysiological function of psoriatic skin cells. Studies have shown that the C19 and C27 peptides bind to CCR4 and activate the MAPK/ERK pathway^[68] [Figure 2].

CMTM1

Calcium (Ca²⁺) plays an important role in the pathogenesis of autoimmunity and inherited immunological dysregulation. Ca²⁺, as a second messenger, regulates many cell functions including gene transcription, apoptosis, and the immune response.^[69] Previous studies have shown that intra-cellular Ca²⁺ signaling plays a role in the pathogenesis of RA.^[70] Rheumatoid arthritis synovial fibroblasts (RASFs) are important effector cells that cause joint inflammation and deformities.^[71] While studying the mechanism of celastrol in RA, Liu *et al*^[72] found that the expression of CMTM1 was down-regulated in RASFs from patients treated with celastrol. They further found that celastrol treatment mobilized cytosolic Ca²⁺ in RASFs. As described, a regulatory role exists for celastrol-induced Ca²⁺ signaling in synovial fibroblasts of RA patients. Wong *et al*^[73] also reported that CMTM1 may be suppressed by calmodulin.

CMTM2

In 2007, Kuttapitiya *et al*^[74] used a detailed histologic and microarray analysis to investigate knee OA bone marrow lesions. They found that the expression of CMTM2 was down-regulated in OA patients compared with healthy controls.^[74] Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by progressive fibrosis of the skin and internal organs.^[75] Previous studies indicated that SSc was associated with multiple susceptibility genes including *HLA-classII*, *PTPN22*, *IRF5*, and *STAT4*. While determining if polymorphisms in the *C8orf13-BLK* region were associated with SSc, Gourh *et al*^[76] discovered that CMTM2 was differentially expressed in SSc peripheral blood cells between rs2736340-rs13277113 heterozygotes versus homozygotes. Pimentel-Santos *et al*^[77] used a whole-genome microarray approach to identify candidate genes associated with AS and to measure gene expression changes occurring during the disease process. They discovered that CMTM2 was up-regulated in the peripheral blood of AS patients.^[77]

CMTM3

Sjögren syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in significant reduction of saliva and tear production.^[78] In 2011, Hu *et al*^[79] utilized a protein microarray approach to identify salivary autoantibody biomarkers for primary SS (pSS). They reported that there was an elevated interaction of CMTM3 with autoantibodies in SLE and pSS patients compared with those from healthy control subjects.^[79]

CMTM4

Encore is an open source network analysis pipeline for genome-wide association studies and rare variant data. To demonstrate Encore utility in the analysis of genetic sequencing data, Davis *et al*^[80] analyzed the exome resequencing data from healthy individuals and those with SLE. They found a novel candidate gene, *CMTM4*, associated with their epistasis network model of the exome data.^[80] Variability in DNA methylation levels contributes to recruitment and expression balance of inflammatory cytokines and to the development of autoimmune diseases. A better understanding of cytokine methylation variation among autoimmune diseases will help to identify potential epigenetic biomarkers and therapeutic targets.^[81] Wang *et al*^[81] reported that the methylation status of the *CMTM4* promoter was significantly different in SLE, RA, and pSS.

CMTM5

The pathogenesis of lupus remains unclear. Dysregulation of gene expression, accompanied by accumulation of abnormal transcripts, may lead to apoptosis or increased expression of IFN-1.^[82] In SLE patients, sense-antisense duplex RNA can drive IFN-1 expression and antisense transcripts can regulate *cis* transcription.^[83] Shi *et al*^[84] found approximately 5000 coding genes had antisense transcription strands in monocytes of SLE. The antisense transcriptional activity of *CMTM5* was much higher compared with sense transcription in SLE patients.^[84] *CMTM5* may contribute to the immunologic dysregulation observed in SLE. As mentioned above, variabilities in methylation status of inflammatory cytokines play an important role in autoimmune diseases. Wang *et al*^[81] also found that *CMTM5* was hypermethylated in SLE and pSS, but hypomethylated in RA.

CMTM6

Anti-phospholipid syndrome (APS) is an autoimmune disorder characterized by arterial and/or venous thrombosis, pregnancy morbidity, and the presence of anti-phospholipid antibodies.^[85] Previous studies have suggested that neutrophils are involved in the pathogenesis of APS. Neutrophil extracellular traps (NETs) play an important role in APS because neutrophils of APS patient are prone to spontaneous NET release.^[86] Recently, Knight *et al*^[87] found that *CMTM6* was up-regulated in the neutrophils of APS patients.

CMTM7, CMTM8

At present, *CMTM7* and *CMTM8* have been identified primarily in tumor and cardiovascular diseases.^[88-90] There are no relevant reports with respect to their involvement in immunologic diseases.

Several studies have indicated that CMTMs have a significant association with tumorigenesis and metastasis. For example, *CMTM7* promotes the internalization of epidermal growth factor receptor (EGFR) and inhibits cell proliferation and metastasis. With respect to protein kinase

(AKT) and ERK activation, Liu *et al*^[91] found that CMTM7 down-regulated AKT phosphorylation and inhibited ERK activation in KYSE180 cells, thus inhibiting EGFR activation of downstream targets.^[91] Previous studies concluded that cancer and autoimmune diseases represent fundamentally different pathological conditions. The fact that cancer and autoimmune diseases may sometimes occur in the same person indicates that there may be a connection between these two different clinical conditions.^[92] The “internal pathway” occurring in tissue cells links cancer with inflammation, thus genetic events that activate oncogenes or inhibit tumor suppressor genes may also lead to the induction of inflammatory proteins. For example, EGFR activation can activate cyclooxygenase-2 by activation of transcription factors Sp1 and p38-MAPK.^[93] Therefore, more studies are needed to define the relationship between CMTM and autoimmune diseases.

At present, a large number of studies have shown that CMTM is closely related to the function of the immune system. CMTM plays an important role in the pathogenesis of many autoimmune diseases. Previous studies have reported that CMTM is highly expressed in the immune system and participates in T cell and B cell activation. However, as a member of the chemokine superfamily, studies on the role of CMTM in autoimmune diseases are limited. The relationship between other family members and autoimmune diseases exists primarily at the level of expression, except for CKLF1 which has been studied in autoimmune diseases. The number of studies showing that CMTM is involved in the occurrence and development of autoimmune diseases has increased. CMTM may be useful as a new prognostic factor or therapeutic target in the future. This will require further understanding of how CMTM participates in the pathogenesis of autoimmune diseases.

Funding

This work was supported by a grant from the National Natural Science Foundation of China (No. 81501390).

Conflicts of interest

None.

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How to cite this article: Duan HJ, Li XY, Liu C, Deng XL. Chemokine-like factor-like MARVEL transmembrane domain-containing family in autoimmune diseases. *Chin Med J* 2020;133:951–958. doi: 10.1097/CM9.0000000000000747