Possible effects of chemokine-like factor-like MARVEL transmembrane domain-containing family on antiphospholipid syndrome

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Abstract
Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic or obstetrical events and persistent antiphospholipid antibodies (aPLs). Chemokine-like factor-like MARVEL transmembrane domain-containing family (CMTM) is widely expressed in the immune system and may closely related to APS. This review aimed to systematically summarize the possible effects of CMTM on APS. Publications were collected from PubMed and Web of Science databases up to August 2020. CKLF, CKLFSF, CMTM, antiphospholipid syndrome, immune cells, and immune molecules were used as search criteria. Immune cells, including neutrophil, dendritic cells (DCs), T-cells, B-cells, and inflammatory cytokines, play an important role in the development of APS. Chemokine-like factor 1 (CKLF1) has a chemotactic effect on many cells and can affect the expression of inflammatory cytokines and adhesion molecules through the nuclear factor-κB (NF-κB) pathway or mitogen-activated protein kinase (MARK) pathway. CKLF1 can participate in the maturation of DCs, T lymphocyte activation, and the activation of neutrophils through the MAPK pathway. CMTM1 may act on Annexin A2 by regulating Ca2+ signaling. CMTM2 and CMTM6 are up-regulated in neutrophils of APS patients. Some CMTM family members influence the activation and accumulation of platelets. CMTM3 and CMTM7 are binding partners of B-cell linker protein (BLNK), thereby linking B cell receptor (BCR) and activating BLNK-mediated signal transduction in B cells. Moreover, CMTM3 and CMTM7 can act on DCs and B-1a cell development, respectively. CMTM may have potential effects on the development of APS by acting on immune cells and immune molecules. Thus, CMTM may act as a novel prognostic factor or immunomodulatory treatment option of APS.

Keywords: Antiphospholipid syndrome; CMTM; Pathogenesis

Introduction
Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic or obstetrical events and persistent antiphospholipid antibodies (aPLs), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β2 glycoprotein-I (β2GPI) antibodies. APS can occur as an isolated diagnosis (primary APS) or can be associated with systemic lupus erythematosus (SLE) or another rheumatic disease. The presence of aPLs plays a critical role in the pathogenesis of APS but is not sufficient for the clinical manifestations of APS. Further insight is needed to identify the pathogenically relevant underlying mechanisms of APS.

Chemokine-like factor superfamily members (CKLFSF) were first cloned and described by the Peking University Human Disease Gene Research Center in 2001. Chemokine-like factor 1 (CKLF1) was isolated from a leukemia cell line U937 after the use of phytohemagglutinin (PHA), and cloned and validated CKLF-like MARVEL transmembrane domain-containing members (CMTM) by reverse transcription PCR. In 2005, according to the molecular structures, the International Human Genetics Nomenclature Committee renamed CKLFSF1-8 to CMTM1-8. CMTM comprises nine genes, CKLFs and CKLFSF1-8, which are located on different chromosomes. CKLF and CMTM1-4 are co-located on chromosome 16q22.1, CMTM5 is independently located on 14q11.2, and CMTM6-8 are co-located on chromosome 3p23 [Figure 1A]. Their gene products include chemokines and the transmembrane 4 superfamily (TM4SF). CMTM1 is most similar to chemokines in particular, whereas CMTM8 resembles TM4SF, and the biological characteristics of CMTM2-7 are somewhere in between.
Various studies have shown that CMTM family members are widely expressed throughout the immune system, exhibit critical functions in the immune system, and are closely related to autoimmune diseases, such as APS. This review aimed to systematically summarize the possible effects of CMTM on APS. CMTM members may be promising targets for the diagnosis and treatment of APS.

Pathogenesis of APS

APS is a systemic autoimmune disease characterized by the persistent presence of aPL, which is defined as LAC and/or significant titers of IgG and/or IgM class aCL and/or IgG and/or IgM class anti-β2GPI in the classification criteria, as a serologic hallmark, and obstetric complications or thrombosis as clinical criteria. The obstetric complications include recurrent early abortions, fetal loss, and premature birth due to (pre-)eclampsia or recognized features of placental insufficiency. The presence of aPLs is necessary, but not sufficient for the clinical manifestations of APS. In recent years, further insight has been provided into relevant mechanisms of pathogenesis of APS. Growing evidence has suggested a role of innate immune cells, in particular neutrophils and dendritic cells (DCs), and adaptive immune cells in APS. Neutrophil activation, including the expression of TF and the release of neutrophil extracellular traps (NETs), and interleukin-8 (IL-8), may be an important factor of aPL-associated thrombosis. DCs play an important role in the sustained production of aPLs triggered by endothelial
B-cell activating factor (BAFF), which is crucial for B-cell survival, may play a role in the prevention of thrombosis associated with APS. Furthermore, T-cell plays an important role in the activation of endothelial cells, thrombocytes, and placental tissue by anti-β2GPI antibodies related to clinical manifestations of APS.

Features of CMTM Family Members

CKLF1

CKLF1 (GenBank accession No. AF096895) maps to chromosome 16q 22.1 and composed of four exons and three introns, with a calculated molecular mass of 10.9 KD [Figure 1B]. The full-length cDNA of CKLF1 is 530 bp long, with a single open reading frame encoding 99 amino acid residues, forming a highly hydrophobic alkaline protein. CKLF1 has the remarkable characteristics of the CC chemokines family and bears two successive cysteine residues in the sequence but does not have an obvious homology as a classical CC subfamily members. Mature CKLF1 protein only contains a single conserved CC motif and lacks the additional C-terminus cysteine.

The CKLF1 motif shares similar amino acids with the thymus, and activation-regulated chemokine (TARC)/C-C class chemokine (CCL) 17 and macrophage-derived chemokine (MDC)/CCL22, which are specific ligands for C-C chemokine receptor 4 (CCR4). Several studies have shown that CKLF1 is a functional ligand for CCR4 and shows a high affinity for CCR4. C19 and C27 are the main secreted forms of CKLF1 at the C-terminus, both of which can interact with CCR4. C27 acts as an agonist of CCR4, whereas C19 acts as an antagonist.

CMTM1-4

CKLF and CMTM1-4 are grouped on chromosome 16q22.1 to form a gene cluster. CMTM1 comprises seven exons, six introns, and 23 isoforms. CMTM2 is tightly linked to CMTM1 [Figure 1C]. CMTM3 [Figure 1D] is highly expressed in multiple immune cells, such as resting B lymphocytes, CD4+T lymphocytes, and monocytes. CMTM3 can enhance Rab5 activity, which plays important roles in T cell receptor (TCR), B cell receptor (BCR), and Toll-like receptors (TLRs). It is suggested that CMTM3 may play a role in the development of autoimmune diseases by promoting Rab5 activity.

CMTM4, with a MARVEL domain and a four-time transmembrane structure, has three transcript variants, such as CMTM4-v1, CMTM4-v2, and CMTM4-v3, of which CMTM4-v2 is the full-length cDNA product and has been highly conserved during evolution. CMTM4 contains four exons and three introns and the last exon can be divided into three parts; that is, A, B, and C. CMTM4-v2 contains all exons, whereas CMTM4-v1 contains exons 1, 2, 3 and part A and part C of exon 4 [Figure 1E].

CMTM5

CMTM5 is independently located on 14q11.2 and closely linked to the interleukin 25 gene. CMTM5 comprises at
least six mRNA splicing bodies, CMTM5-v1-v6, of which CMTM5-v1 is the most conserved.\textsuperscript{[3]}

**CMTM6-8**

CMTM6-8 is located in a gene cluster on chromosome 3p22. CMTM6, adjacent to CMTM7, is 21,600 nucleotides long and encodes three transcripts, CMTM6-001 to CMTM6-003, but only CMTM6-001 bearing four introns can be successfully translated. CMTM6 is a 183 amino acid protein with a typical MARVEL domain.\textsuperscript{[3]} CMTM7 is located between CMTM6 and CMTM8, within the same cluster, and is 63858 bp in length [Figure 1A]. CMTM7 is highly expressed in leukocytes and has six splicing isoforms: CMTM7-001 to CMTM7-006. CMTM7-001 is the main splicing isoform and can be detected by Northern blot analysis, and its cDNA is 1369 bp long, including four introns, five exons, a classical promoter sequence, and a poly (A) tail.\textsuperscript{[30]} The cDNA of CMTM5 has a full length of 1185bp, of which nucleotides 295–816 encode CMTM8. The expression product is a four-time transmembrane protein, which consists of 173 amino acids and MARVEL domains for vesicular transport and membrane ligation [Figure 1F].\textsuperscript{[1]}

**Possible Effects of the CMTM Family on APS**

**Endothelial cells**

The aPL can bind to the immunogenic β2GPI, thereby resulting in endothelial-cell activation, and causing some proinflammatory and prothrombotic changes.\textsuperscript{[20–22]} The presence of aPL may up-regulate cell-surface adhesive molecules (such as ICAM-1) and stimulate the release of TNF-α.\textsuperscript{[19]} CKLF1 has a broad spectrum of chemotactic activity and can affect the expression of inflammatory cytokines and adhesion molecules.\textsuperscript{[40]} Kong et al.\textsuperscript{[41]} reported that an anti-CKLF1 antibody could decrease the production of inflammatory factors TNF-a, IL-1b, macrophage inflammatory protein-2, and IL-8 as well as that of adhesion molecules, ICAM-1, and vascular cell adhesion molecule 1 (VCAM-1). Furthermore, CMTM3 possesses the capability of mediating intercellular adhesion at endothelial adherens junctions, which play a key role in maintaining endothelial barrier function, through participating in VE-cadherin turnover and regulating the cell surface pool of VE-cadherin.\textsuperscript{[42]}

NF-κB plays an important role in the intracellular signaling cascade of the classic complement activation pathway in APS.\textsuperscript{[23,24]} Targeting NF-κB is a therapeutic option.\textsuperscript{[43]} It has been reported that CKLF1 can activate the NF-κB signaling pathway, which can regulate the expression of pro-inflammatory mediators. Keith et al.\textsuperscript{[44]} showed that WAY-169916, a selective NF-κB transcriptional inhibitor, caused a marked decrease in CKLF1 expression in the rat spleen. Thus, CKLF1 may act on inflammation through the NF-κB pathway.

Calcium (Ca\textsuperscript{2+}) plays an important role in the pathogenesis of autoimmune diseases.\textsuperscript{[13]} In the presence of Ca\textsuperscript{2+}, Annexin A2 is associated with anionic phospholipid and participates in the thrombosis of APS.\textsuperscript{[45]} Liu et al.\textsuperscript{[46]} demonstrated that the expression of CMTM1 was down-regulated in rheumatoid arthritis synovial fibroblasts (RASFs) from rheumatoid arthritis (RA) patients treated with celestrol, which can induce Ca\textsuperscript{2+} signaling and mobilize cytosolic Ca\textsuperscript{2+} in RASFs. In addition, Wong et al.\textsuperscript{[47]} showed that CMTM1 may be suppressed by calmodulin. Moreover, CMTM1-v3 can interact with calcium-modulating cyclophilin ligand (CAML), which can negatively participate in the intracellular calcium signaling to negatively regulate the Ca\textsuperscript{2+} response in the endoplasmic reticulum (ER), thereby causing an increase in calcium influx and in turn activating the calcineurin, leading to the activation of NF-κB.\textsuperscript{[48]} Therefore, CMTM1 can play a role in the regulation of Ca\textsuperscript{2+} signaling and accordingly act on Annexin A2.

**Platelets**

*In vitro*, aPLs can act on platelets from healthy donors and increase the expression of glycoprotein IIb/IIIa (the receptor for fibrinogen).\textsuperscript{[49,50]} Platelets may play a key role in the prothrombotic interactions between aPLs and endothelial cells in APS.\textsuperscript{[22]}

The CMTM family may influence the activation and accumulation of platelets and play a role in the process of hemostasis and thrombosis. Through paired-end next-generation RNA sequencing to identify functional differences in platelets of human and mouse, it was suggested that CMTM5 can be expressed in human platelets, but not in mouse platelets.\textsuperscript{[51]} Platelets possess palmitoylization machinery that is required for both platelet activation and platelet accumulation into thrombi.\textsuperscript{[52]} Dowal et al.\textsuperscript{[53]} showed that CMTM3, CMTM5, and CMTM7 were significantly enriched in the hydroxyamine+ (HA+) sample, which suggested that they were palmitoyl proteins. CMTM3, CMTM5, and CMTM7 may play a specific role in platelet function and be potential targets for the modulation of hemostasis and thrombosis. Moreover, the expression of CKLF, CMTM1-3, and CMTM5-7 is up-regulated in platelets of SLE patients when compared to those of healthy individuals, implying that they may affect platelet activation and contribute to the development of vascular disease in SLE.\textsuperscript{[54]}

**Innate immunity cells**

**DCs**

The presence of DCs, the most potent antigen-presenting cells that link innate and adaptive immunity, is necessary for generating and maintaining the production of aPLs triggered by exposed intracellular phospholipids on the outer surface of apoptotic cells in APS.\textsuperscript{[27]}

In previous studies, Shao et al.\textsuperscript{[55]} showed that CKLF1 was highly expressed in monocytes. During differentiation from monocytes to immature DCs, CKLF1 was significantly increased on day 2, then decreased from day 3 to 5. CKLF1 was down-regulated upon the maturation of DCs activated by different stimuli. Hence, CKLF1 plays a key role in the maturation of DCs.\textsuperscript{[55]} Two peptides of CKLF1, C19, and C27 can promote the effect of immature DCs
(imDCs) on T-cell proliferation and IFN-γ production. In addition, they up-regulate the secretion of HLA-DR and IL-12, without obvious effects on CD80, CD83, or CD86 in immature DCs. Thus, CKLF1-C19 and -C27 stimulate the antigen-presenting capability of imDCs.\textsuperscript{[55]} B-cell linker protein (BLNK) has distinct functions in endocytosis and signaling through a cell-surface receptor in DCs. It has been reported that CMTM3, as a binding partner of BLNK, is highly expressed in DCs.\textsuperscript{[156]} CMTM3 can also bind to SLP76 in DC2.4 cells. Consequently, CMTM3 may have an important role in DCs via BLNK.\textsuperscript{[57]}

**Neutrophils**

Neutrophils are involved in the pathogenesis of APS. Neutrophil activation, including the expression of TF and the release of NETs and IL-8, may be an important factor of aPL-associated thrombosis.\textsuperscript{[58]}

Previous studies have shown that CKLF1 exhibits a broad spectrum of chemotactic activity on neutrophils and can activate neutrophils through the MAPK pathway.\textsuperscript{[40]} Additional studies showed that when administrated an anti-CKLF1 antibody, numbers of myeloperoxidase (MPO)-positive neutrophils and the activity of MPO, a marker enzyme for measuring neutrophils accumulation, decreased. An anti-CKLF1 antibody can also inhibit the phosphorylation level of p38, extracellular signal-regulated kinase (ERK), and c-Jun-N-terminal kinase (JNK) of the MAPK signal transduction pathway, which are the most important signaling molecules that are thought to mediate inflammatory responses.\textsuperscript{[41,59-61]} Therefore, anti-CKLF1 antibodies can inhibit neutrophil infiltration via acting on MAPK signaling pathways. Recently, Knight et al.\textsuperscript{[62]} showed that CMTM2 and CMTM6 were up-regulated in neutrophils from APS patients.

**Adaptive Immune Cells**

**T-cells**

The protein β2GPI is regarded as the most important autoantigen in APS. By activating endothelial cells, thrombocytes, and placental tissue, T-cell-dependent anti-β2GPI autoantibodies are associated with the development of autoimmune coagulation and obstetric complications in APS.\textsuperscript{[126]}

As mentioned above, CKLF1 is a novel functional ligand of CCR4.\textsuperscript{[126]} CCR4 can facilitate the recruitment, homing, and education of activated leukocytes (mainly CD4+ Th2 lymphocytes).\textsuperscript{[30,63]} In addition, CKLF1 itself has chemotactic effects on leukocytes.\textsuperscript{[40]} Therefore, the interaction of CKLF1 with CCR4 might play a role in T-cells.

CKLF1 may be involved in the activation of T lymphocytes. When studying the expression profile of CKLF1 in activated T lymphocytes, Li et al. demonstrated that CKLF1 was up-regulated in activated CD4+ and CD8+ cells, with no obvious changes in CD19+ cells. They further performed kinetic analyses of CKLF1 expression in PHA-stimulated human peripheral blood lymphocytes (PBL) at both mRNA and protein levels. They found that the expression of CKLF1 in lymphocytes was remarkably up-regulated by PHA, appearing at 8 h after PHA-stimulation and persisting up to 72 h, which showed that it could be up-regulated by PHA-activation in a time-dependent manner.\textsuperscript{[64]}

Furthermore, the expression of CKLF1, as well as that of C-X-C motif chemokine ligand (CXCL)13 and inducible co-stimulator (ICOS), is significantly up-regulated in germinal center T helper cells (GC-Th cells), which are mostly nonpolarized (lacking IL-4 and interferon α [IFN-α] production) but are efficient in inducing B-cell production of immunoglobulin.\textsuperscript{[65]} It has been suggested that CKLF1 may participate in the humoral immune response and germinal center formation via acting on GC-Th cells.

**B-cells**

B-cells serve a central role in the pathophysiology of an autoantibody-mediated disease, such as APS.\textsuperscript{[25]} Increased percentages and absolute counts of naïve B cells were observed in APS women.\textsuperscript{[66]} Moreover, B-cell activating factor (BAFF), which is crucial for B-cell survival, may play a role in the prevention of thrombosis associated with APS.\textsuperscript{[28]}

BLNK is a pivotal adaptor protein in the signal transduction pathway from the IgM class BCR.\textsuperscript{[67-69]} In previous studies, it was identified that CMTM3 was a binding partner of BLNK that could bind the N-terminal part of BLNK.\textsuperscript{[57]} In the chicken B cell line DT40, CMTM3 may act as a scaffold for signaling proteins and enhance ERK activation by BCR signaling. CMTM3 can enhance Rab5 activity, which is a key check-point in the endocytic pathways of BCR trafficking.\textsuperscript{[136]} CMTM7 is also a binding partner of BLNK.\textsuperscript{[57]} CMTM7 can link σ1M and BLNK in the plasma membrane to recruit BLNK to the environment of Syk and to initiate BLNK-mediated signaling transduction. In general, CMTM7 can link BCR and activate BLNK-mediated signal transduction in B cells, specifically involved in BCR expression.\textsuperscript{[57]}

Innate-like B-1a cells (also termed CD5-positive B-cells) are an important cell population for the secretion of natural IgM and IL-1, and they act as the first line against pathogens.\textsuperscript{[70,71]} Increased percentages of B-1a cells in primary APS patients correlated with levels of IgM aPLs.\textsuperscript{[72]} CMTM7 is essential for B-1a cells development. CMTM7 is specifically involved in the survival of B-1a cells and the plasma cell generation of B-1a and B-1b cells, while having little effect on the development and function of B-2 cells.\textsuperscript{[73]} Further investigations demonstrated that CMTM7 specifically acted on the B-1a cell development at the transitional B-1a (TrB-1a) stage. Loss of CMTM7 resulted in B-1a cell developmental arrest at TrB-1a, resulting in reduced numbers of mature B-1a cells in spleen and PerC, followed by the marked decrease of B-1a cell numbers in all investigated tissues, which results from B-cell-intrinsic defects. Because of B-1a cells loss, CMTM7-deficient mice produced less IgM and IL-10 and were more susceptible to microbial sepsis.\textsuperscript{[74]}

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\textsuperscript{40}[62] Knight et al. (2021). The involvement of CMTM2 and CMTM6 in neutrophils from APS patients.
Summary and Prospect

APS has a broad spectrum of thrombotic and non-thrombotic clinical manifestations.\(^1\) The presence of aPLs plays a critical role in the pathogenesis of APS but is not sufficient for the clinical manifestations of APS.\(^2\) Further insight on the pathogenesis of APS is needed.

CMTM family members are widely expressed in the immune system, participate in T cell and B cell activation, and are closely related to autoimmune diseases, such as APS.\(^6,13\) In a large number of studies, it was suggested that CMTM may have potential effects on the development of APS through acting on immune cells and immune molecules [Figure 3]. CKLF1 has a broad spectrum of chemotactic effects on many cells, including lymphocytes, macrophages, and neutrophils.\(^39\) CKLF1s can affect the expression of inflammatory cytokines and adhesion molecules in terms of NF-κB or MAPK pathways.\(^43,56\) CKLF1 plays a key role in the maturation of DCs, as well as on the activation of T lymphocytes, and participates in the humoral immune response and germinal center formation via acting on GC-Th cells.\(^53,62,63\) Furthermore, CKLF1 can activate neutrophils through the MAPK pathway.\(^56\) CMTM1 may act on Annexin A2 by regulating Ca\(^{2+}\) signaling.\(^13,45,46\) CMTM2 and CMTM6 are up-regulated in neutrophils of APS patients.\(^59\) Some CMTM family members may have an effect on the activation and accumulation of platelets and play a role in processes, such as hemostasis and thrombosis.\(^49-52\) CMTM3 and CMTM7 are binding partners of BLNK, linking BCR and activating BLNK-mediated signal transduction in B cells.\(^55\) Furthermore, CMTM3 may play an important role in DCs.\(^54\) CMTM7 is essential for B-1a cells development and specifically acts on the transitional B-1a (TrB-1a) stage.\(^70,71\)

However, relatively a few in-depth studies on CMTM have been performed in APS. Advances in our understanding of how CMTM participates in the pathogenesis of APS are needed. Thus, CMTM may act as a novel prognostic factor or immunomodulatory treatment option of APS in the future.

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**Figure 3:** Potential effects of CMTM on APS. CKLF1 has a chemotactic effect on many cells and can affect the expression of inflammatory cytokines and adhesion molecules through the MAPK pathway. CKLF1 can participate in the maturation of DCs, T lymphocyte activation, and the activation of neutrophils through the MAPK pathway. CMTM1 may act on Annexin A2 by regulating Ca\(^{2+}\) signaling. CMTM2 and CMTM6 are up-regulated in the neutrophils of APS patients. CMTM3, CMTM5, CMTM7 influence the activation and accumulation of platelets. CMTM3 and CMTM7 are binding partners of BLNK, thereby linking BCR and activating BLNK-mediated signal transduction in B cells. CMTM3 and CMTM7 can act on DCs and B-1a cell development, respectively. aPL: Antiphospholipid antibody; β2GPI: β2 glycoprotein-I; β2-GPI surface receptors: Referring to apoER2\(^-\), annexin A2, or a Toll-like receptor; BCR: B cell receptor; BLNK: B-cell linker protein; CKLF1: chemokine-like factor 1; CMTM: Chemokine-like factor-like MARVEL transmembrane domain-containing family; DCs: Dendritic cells; IL: Interleukin; MAPK: Mitogen-activated protein kinase; PMN: Polymorphonuclear neutrophils; TNF-α: Tumor necrosis factor-α.
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