

# CMTM4 as a new partner for IL-17 receptor: adding a piece in the puzzle of IL17-driven diseases

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## Abstract

IL-17 has emerged as an important cytokine in protecting the host from mucosal infections, but also as a pathogenic determinant and therapeutic target in numerous autoimmune and inflammatory diseases (e.g. psoriasis, psoriatic arthritis and ankylosing spondylitis, inflammatory bowel disease and multiple sclerosis) [(1)](#ref-0001). The IL-17 family includes six members (IL-17A to IL-17F) that act through the IL-17 receptors [(1)](#ref-0001). The most studied IL-17A, as well as IL-17F, binds to IL-17RA and IL-17RC resulting in heterodimerization. Currently IL-17A, IL-17F, IL-17RA or IL-23, a cytokine produced by innate immune cells that promotes expansion of Th17 cell populations, are targetable by monoclonal antibodies (mAbs). These mAbs have been approved for the treatment of different autoimmune diseases, most notably psoriasis, where their efficacy has outperformed conventional non-steroidal anti-inflammatory and tumor necrosis factor (TNF) blocking drugs. However, clinical trials and real-life experience have shown an increase in fungal and bacterial upper respiratory tract infections in patients treated with mAbs that block IL-23/IL-17 signaling. Accordingly, single nucleotide polymorphisms in genes encoding IL-17A, IL-17RA, IL-17RC, IL-23, or NF- $\kappa$ B activator 1 (ACT1, an adapter protein downstream of the IL-17R) which abrogate cellular responsiveness to IL-17A, were associated with susceptibility to chronic mucocutaneous candidiasis (CMC), a persistent infection of the skin, nails, and/or mucous membranes with commensal *Candida* species [(2)](#ref-0002). So new effective targeted approaches in IL-17 signaling are desirable. Knizkova and colleagues identified a new adaptor molecule involved in the IL-17/IL-17R cascade [(3)](#ref-0003). Through murine and human cell models, the authors found that CMTM4 (CKLF Like MARVEL Transmembrane Domain Containing 4) constitutively bound to the subunit IL-17RC becoming integral part of the IL-17R signaling complex (IL-17RSC) upon IL-17A stimulation. CMTM4 promoted the surface expression of IL-17RC by regulating posttranslational modifications, especially IL-17RC glycosylation and trafficking to trans-Golgi up to plasma membrane. CMTM4 was required for the recruitment of adapter ACT1, for the activation of p38, JNK and transcription of genes encoding proinflammatory cytokines upon IL-17A stimulation (Figure 1A). Keratinocytes from the tail of *Cmtm4*<sup>-/-</sup> mice specifically express lower levels of IL-17RC respect to *Cmtm4*<sup>+/+</sup> mice (Figure 1B). *In vivo*, when imiquimod (IMQ) was applied on the ears or shaven backs of *Cmtm4*<sup>-/-</sup> mice, they developed less severe psoriatic lesions and lower local expression of IL-17A target genes compared to *Cmtm4*<sup>+/+</sup> mice (Figure 1C).

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IL-17 has emerged as an important cytokine in protecting the host from mucosal infections, but also as a pathogenic determinant and therapeutic target in numerous autoimmune and inflammatory diseases (e.g. psoriasis, psoriatic arthritis and ankylosing spondylitis, inflammatory bowel disease and multiple sclerosis) (1). The IL-17 family includes six members (IL-17A to IL-17F) that act through the IL-17 receptors (1). The most studied IL-17A, as well as IL-17F, binds to IL-17RA and IL-17RC resulting in heterodimerization. Currently IL-17A, IL-17F, IL-17RA or IL-23, a cytokine produced by innate immune cells that promotes expansion of Th17 cell populations, are targetable by monoclonal antibodies (mAbs). These mAbs have been approved for the treatment of different autoimmune diseases, most notably psoriasis, where their efficacy has outperformed conventional non-steroidal anti-inflammatory and tumor necrosis factor (TNF) blocking drugs. However, clinical trials and real-life experience have shown an increase in fungal and bacterial upper respiratory tract infections in patients treated with mAbs that block IL-23/IL-17 signaling. Accordingly, single nucleotide polymorphisms in genes encoding IL-17A, IL-17RA, IL-17RC, IL-23, or NF- $\kappa$ B activator 1 (ACT1, an adapter protein downstream of the IL-17R) which abrogate cellular responsiveness to IL-17A, were associated with susceptibility to chronic mucocutaneous candidiasis (CMC), a persistent infection of the skin, nails, and/or mucous membranes with commensal *Candida* species (2). So new effective targeted approaches in IL-17 signaling are desirable.

Knizkova and colleagues identified a new adaptor molecule involved in the IL-17/IL-17R cascade (3). Through murine and human cell models, the authors found that CMTM4 (CKLF Like MARVEL Transmembrane Domain Containing 4) constitutively bound to the subunit IL-17RC becoming integral part of the IL-17R signaling complex (IL-17RSC) upon IL-17A stimulation. CMTM4 promoted the surface expression of IL-17RC by regulating posttranslational modifications, especially IL-17RC glycosylation and trafficking to trans-Golgi up to plasma membrane. CMTM4 was required for the recruitment of adapter ACT1, for the activation of p38, JNK and transcription of genes encoding proinflammatory cytokines upon IL-17A stimulation (Figure 1A). Keratinocytes from the tail of *Cmtm4*<sup>-/-</sup> mice specifically express lower levels of IL-17RC respect to *Cmtm4*<sup>+/+</sup> mice (Figure 1B). *In vivo*, when imiquimod (IMQ) was applied on the ears or shaven backs of *Cmtm4*<sup>-/-</sup> mice, they developed less severe psoriatic lesions and lower local expression of IL-17A target genes compared to *Cmtm4*<sup>+/+</sup> mice (Figure 1C). However, in a MOG-induced model of experimental autoimmune encephalomyelitis (EAE), *Cmtm4*<sup>-/-</sup> mice displayed an only slightly milder EAE progression compared to *Cmtm4*<sup>+/+</sup> littermates, and the difference was not statistically significant (Figure 1D). Overall, CMTM4 regulated IL-17A signaling *in vivo* and mediated psoriasis, while it had only a limited role in EAE. These apparently controversial results can be explained by the fact that EAE pathology is not exclusively driven by IL-17 and Th17 cells, but other cytokines and cells, including CD8+ T cells and Th1 cells, fibroblasts, pericytes and astrocytes may be involved (4,5). Indeed, as it displayed a relatively broad tissue distribution, CMTM4 might finely tune the expression of other proteins, not strictly connected to the immune compartment where CMTM4 is missing, influencing the EAE disease course (5). Accordingly, anti-IL-17 mAb treatment significantly reduced clinical scores when administered at induction but not after clinical symptom onset in the EAE model (6). This because while IL-17 is required to trigger inflammation, it is superfluous in the effector stage of the disease (6). These aspects could further explain the mild effects of the lack of CMTM4 on EAE pathogenesis.

In summary, the study by Knizkova and colleagues adds a new piece in the puzzle of IL-17/IL-17R pathway, since highlights CMTM4 as an essential subunit of the IL-17R, required for the IL-17R signaling. Given its role in mediating IL-17A-induced responses, CMTM4 could represent a potential new target for the therapy of IL-17A-mediated autoimmune diseases. On the other hand, it is necessary to take into consideration that CMTM4 increases stability of PD-L1 protein, thus targeting CMTM4 could impair PD-1/PD-L1 axis as well. Moreover, *Cmtm4* could also represent another putative gene whose defects or SNPs could account for unexplained increased susceptibility to CMC.

## Figure 1

(A) CKLF Like MARVEL Transmembrane Domain Containing 4 (CMTM4) protein adapter is constitutively and specifically associated to IL-17 receptor C (IL-17RC) and it is essential for full glycosylation of the receptor molecule and the trafficking to trans-Golgi up to plasma membrane. Upon IL-17A stimulation, IL-17RC forms heterodimer with IL-17 receptor A (IL-17RA) and activates intracellular signaling cascade. (B) In *Cmtm4*<sup>-/-</sup> mice the expression of IL-17RC is specifically downregulated in the keratinocytes. (C) In Imiquimod (IMQ)-induced psoriasis mouse model, *Cmtm4*<sup>-/-</sup> mice developed less severe psoriatic lesions and lower local expression of IL-17A target genes compared to *Cmtm4*<sup>+/+</sup> mice. (D) MOG-induced model of experimental autoimmune encephalomyelitis (EAE), *Cmtm4*<sup>-/-</sup> and *Cmtm4*<sup>+/+</sup> mice displayed comparable EAE severity score.

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## CONFLICT OF INTEREST

None of the authors have a conflict of interest to disclose.

## REFERENCES

1. Mills KHG. IL-17 and IL-17-producing cells in protection versus pathology. *Nat Rev Immunol* 2023;**23** (1):38-54.
2. Li J, Vinh DC, Casanova JL, Puel A. Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals. *Curr Opin Microbiol* 2017;**40** :46-57.
3. Knizkova D, Pribikova M, Draberova H, Semberova T, Trivic T, Synackova A, et al. CMTM4 is a subunit of the IL-17 receptor and mediates autoimmune pathology. *Nat Immunol* 2022;**23** (11):1644-1652.
4. Kroenke MA, Carlson TJ, Andjelkovic AV, Segal BM. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. *J Exp Med* 2008;**205** (7):1535-1541.
5. Dorrier, C.E., Jones, H.E., Pintarić, L. *et al.* Emerging roles for CNS fibroblasts in health, injury and disease. *Nat Rev Neurosci* **23** , 23–34 (2022). <https://doi.org/10.1038/s41583-021-00525-w>
6. McGinley AM, Sutton CE, Edwards SC, Leane CM, DeCoursey J, Teijeiro A, et al. Interleukin-17A Serves a Priming Role in Autoimmunity by Recruiting IL-1beta-Producing Myeloid Cells that Promote Pathogenic T Cells. *Immunity* 2020;**52** (2):342-356 e346.

