Immunology & Cell Biology 2023; **101**: 600–609
www.wileyonlinelibrary.com/journal/icb

REVIEW

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CCL17/TARC in autoimmunity and inflammation—not just a T-cell chemokine

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Keywords
Autoimmunity, CCL17, chemokine, inflammation, pain, therapy

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Received 5 October 2022;
Revised 16 January and 21 March 2023;
Accepted 26 March 2023

doi: 10.1111/imcb.12644

Immunology & Cell Biology 2023; **101**: 600–609

Abstract

Chemokine (C–C) ligand 17 (CCL17) was first identified as thymus- and activation-regulated chemokine when it was found to be constitutively expressed in the thymus and identified as a T-cell chemokine. This chemoattractant molecule has subsequently been found at elevated levels in a range of autoimmune and inflammatory diseases, as well as in cancer. CCL17 is a C–C chemokine receptor type 4 (CCR4) ligand, with chemokine (C–C) ligand 22 being the other major ligand and, as CCR4 is highly expressed on helper T cells, CCL17 can play a role in T-cell–driven diseases, usually considered to be *via* its chemotactic activity on T helper 2 cells; however, given that CCR4 is also expressed by other cell types and there is elevated expression of CCL17 in many diseases, a broader CCL17 biology is suggested. In this review, we summarize the biology of CCL17, its regulation and its potential contribution to the pathogenesis of various preclinical models. Reference is made, for example, to recent literature indicating a role for CCL17 in the control of pain as part of a granulocyte macrophage–colony-stimulating factor/CCL17 pathway in lymphocyte-independent models and thus not as a T-cell chemokine. The review also discusses the potential for CCL17 to be a biomarker and a therapeutic target in human disorders.

INTRODUCTION

Chemokine (C–C) ligand 17 (CCL17), which is also known as thymus- and activation-regulated chemokine, was first discovered as a constitutively expressed protein in the thymus by Imai *et al.* in 1996.[1] Its designation originally arose from its chemotactic activity on C–C chemokine receptor type 4–positive ($CCR4^+$) cells, which are predominately T cells.[2] CCL17 is secreted by many cell types and its levels have since been found to be elevated in a wide range of diseases, including T helper 2 (Th2) diseases, such as atopic dermatitis (AD) and asthma, and autoimmune diseases, such as rheumatoid arthritis (RA). In this short review the diverse biology of CCL17 and its roles in various autoimmune and inflammatory diseases will be discussed, as well as its potential to be a diagnostic biomarker and therapeutic target. While CCL17 shares its receptor with chemokine (C–C) ligand 22 (CCL22), which is also elevated in autoimmune and inflammatory diseases, the focus here will be on CCL17 biology.

CCL17 BIOLOGY

CCL17 gene and protein structure

The human *CCL17* gene is encoded on chromosome 16q13, and it is made up of 2176 bp and 4 exons.[3] The human CCL17 monomer is an 8.1-kDa protein composed of 71 amino acids and a 23-amino acid signal peptide[3]; the CCL17 dimer has a unique asymmetrical structure that is not seen in the other C–C chemokines.[3,4]

CCL17 binding to CCR4

CCR4 belongs to the G protein–coupled receptor family with CCL17 and CCL22 being considered as its major

ligands. CCL22 is also a chemokine that is highly expressed in the thymus.[5] The interaction of CCL17 with CCR4 is often compared with that of CCL22. CCR4 is reported to have at least two distinct binding conformations and CCL17 can bind only to the major conformation, while CCL22 can bind to both the major and minor conformations.[6] CCL17 also binds to CCR4 with lower affinity than CCL22,[7] and it is less effective at inducing receptor internalization, chemotaxis and beta-arrestin coupling in $CCR4^+$ cells[8–10]; CCL22 potently desensitizes CCR4 to CCL17 in Th2 cell types,[10] although the opposite was seen in regulatory T cells (Tregs), whereby CCL17 desensitizes CCR4 to CCL22 in a dose-dependent manner.[11] The unique binding characteristics of CCL17 to CCR4 induce downstream signaling when it is concurrently bound to two of its binding sites.[6,12] As CCL17 and CCL22 have different and even competing effects on CCR4, in this short review our focus is on CCL17 biology *per se* rather than on CCR4 and CCL22. Therapies can be designed to specifically target CCL17 function while leaving those of CCL22 and CCR4 intact.

CCL17 as a chemotactic agent

The biology of CCL17 is often associated with T cells as its receptor, CCR4, is predominately expressed by Th2 cells, although it is also expressed by T helper 17, T helper 22, Tregs cells, natural killer cells, type 2 $CD8^+$ T cells and cutaneous lymphocyte antigen–expressing skin-homing T cells.[2] CCR4 is also expressed by other cell types, such as airway eosinophils, megakaryocytes and platelets, and so the migration of these cells could also be regulated by CCL17 in certain contexts.[2] Moreover, CCL17 may enhance the chemotactic functions of other chemokines. In one mouse model of dermal inflammation, it was shown that CCL17 is indirectly required for C–C chemokine receptor type 7 (CCR7)- and CXCR4-dependent migration of cutaneous dendritic cells (DCs),[13] while another study using a murine vaccination model showed that CCL17 is required for chemokine (C–C) ligand 19–dependent migration of mature $CCR7^+$ DCs.[14] While CCL17 may not directly bind to CCR7, it might indirectly regulate its migration.

Cellular expression and regulation of CCL17 synthesis

CCL17 expression is not limited to the thymus and it is produced by a number of different cell types in various tissues. These cells include monocytes, macrophages, DCs, eosinophils, epithelial cells (e.g. keratinocytes), Langerhans cells, fibroblasts, platelets and various T cells.[15,16] The chemokine is synthesized in various tissues, such as the thymus, lymph nodes, gut, bronchi and the brain, and is found in the circulation and in the lymphatic system.[16,17]

The molecular mechanisms underlying CCL17 synthesis and secretion differ depending on the cell type and nature of the stimulus, and the chemokine was suggested to be able to regulate its own production in $CCR4^+$ DCs in an autocrine manner.[18] In immune cells, interleukin-4 (IL-4) can stimulate CCL17 synthesis *via* (i) signal transducer and activator of transcription 6 phosphorylation, whereby the activated dimer can directly bind to the CCL17 promoter[19], (ii) the demethylase activity of Jumonji domain-containing 3 protein D3 (JMJD3) and interferon regulatory factor 4[20] and (iii) the mitogen-activated protein kinase kinase (MEK)5/extracellular signal-regulated kinase (ERK)5 signaling pathway.[21] IL-4 can also cooperate with IL-3, interferon-gamma and tumor necrosis factor to synergistically upregulate CCL17 expression.[16]

In addition, CCL17 production by interferon-gamma and tumor necrosis factor is nuclear factor-kappa B– and signal transducer and activator of transcription 1–dependent (see, for example, Saeki and Tamaki[22]), which is consistent with the presence of consensus recognition sequences of interferon-gamma response elements[23] and potential nuclear factor-kappa B transcriptional elements in the CCL17 promoter.[24] Given that many cytokines can activate nuclear factor-kappa B signaling, other inflammatory cytokines are likely to regulate CCL17 expression.

The granulocyte macrophage–colony-stimulating factor/CCL17 pathway

It has also been shown that granulocyte macrophage–colony-stimulating factor (GM-CSF), a hematopoietic growth factor and proinflammatory cytokine, upregulates CCL17 production *via* JMJD3 and interferon regulatory factor 4 in human monocytes and mouse macrophages (termed the GM-CSF/CCL17 pathway).[25] GM-CSF–activated signal transducer and activator of transcription 5 can also directly bind to the CCL17 promoter to regulate its expression.[26]

In preclinical models of inflammation, when GM-CSF activity was neutralized with a monoclonal antibody (mAb), CCL17 expression was inhibited in inflammatory macrophages and monocyte-derived DCs.[25,27] It was also demonstrated that the GM-CSF/CCL17 pathway is relevant in T-cell independent, inflammatory arthritic[25,28] and osteoarthritic pain[29,30]; as CCL17 is usually associated with T-cell biology, these studies[25,28–30] highlight a novel, non-T–cell biology for the chemokine. Furthermore, it was noted in arthritis models that CCL17 deletion/depletion can have minimal effects on cell infiltration into the joints, despite having a dramatic

effect on pain; in other words, CCL17 seems to have a broader role than simply being a chemokine.[25,28,29]

The GM-CSF/CCL17 pathway has also been demonstrated in humans. In clinical trials for RA, circulating CCL17 levels were significantly reduced in patients treated with otilimab, a GM-CSF–targeting mAb, and with mavrilimumab, a GM-CSF receptor–targeting mAb.[31,32] The presence of this GM-CSF/CCL17 pathway could lead to a new diagnostic approach, in that high CCL17 levels in patients could serve as a biomarker to justify anti-GM-CSF–based therapeutics for various indications, leading hopefully to better clinical outcomes.

As indicated earlier, elevated CCL17 levels are seen in a number of diseases, some of which are discussed in the next section.

CCL17 in disease

Rheumatoid arthritis

RA is a chronic inflammatory, autoimmune joint disease, with its pathogenesis involving inflammatory cell infiltration, elevated proinflammatory cytokine levels and irreversible joint destruction. It has been reported that CCL17 is detected in the synovial fluid of patients with RA.[33,34] Interestingly, one study indicated no difference in CCL17 serum expression between patients with RA and healthy volunteers,[35] although it was not indicated as to whether these patients were receiving treatment and thus warrants further investigation. CCL17 has been shown to be secreted by mononuclear cells in RA synovial fluid, including $CD1c^+$ DCs.[34,36]

In animal models of inflammatory arthritis, including zymosan-induced and antigen-induced arthritis, *CCL17* gene–deficient mice fail to develop arthritic pain and optimal disease, and the therapeutic administration of anti-mouse CCL17 mAb ameliorates already established arthritic pain and halts disease progression.[25,28] Systemically administered CCL17 has also been shown to directly induce arthritic pain and disease in methylated bovine serum albumin (BSA)-injected joints, as well as inflammatory pain in mouse paws, with the CCL17-driven inflammatory pain dependent on cyclooxygenase activity, neurotrophins and neuropeptides.[27] These studies indicate a role for CCL17 in the development and progression of inflammatory arthritic pain; however, whether CCL17 acts on neurons directly *via* CCR4 remains controversial, as one study claimed that peripheral sensory neurons express CCR4,[37] while another study using single-cell RNA-seq detected no *CCR4* expression by these cells.[38]

As mentioned earlier, patients with RA who receive neutralizing mAbs against GM-CSF or its receptor have reduced circulating CCL17 levels[31]; these findings are consistent with a functional GM-CSF/CCL17 pathway and serve as supporting evidence for CCL17 to be considered as a biomarker for anti-GM-CSF or anti–GM-CSF receptor treatment in RA and possibly other inflammatory arthritides. Furthermore, as GM-CSF deficiency can potentially lead to the lung condition known as pulmonary alveolar proteinosis,[39] targeting CCL17 may be an alternative and safer therapeutic target.

Osteoarthritis

Osteoarthritis (OA) was once considered to be a noninflammatory arthropathy; however, it is now well-recognized that there is a significant inflammatory component in its pathogenesis and in the development of symptoms, including chronic pain.[40] Interestingly, increased CCL17 levels have been associated with increased pressure pain sensitivity and higher pain intensity in male patients with OA.[41]

Preclinical studies have demonstrated that *CCL17* gene–deficient mice are protected from the development of collagenase-induced OA pain and optimal disease,[29] and the therapeutic neutralization of CCL17 effectively ameliorates pain and disease progression in the same OA model.[29,30] Synovial macrophages were shown to be a major cellular source of CCL17 in this model.[29] Moreover, mice induced with this OA model, that were also *GM-CSF*-deficient or treated with anti-GM-CSF mAb, had a reduction in pain that was similar to that seen with CCL17 blockade.[30] These findings point toward the potential relevance of the GM-CSF/CCL17 pathway in OA; however, the effect of CCL17 inhibition on OA pain needs to be investigated in other OA models. In addition, OA is a multifactorial disease with many risk factors, such as aging and obesity[40]; the role of CCL17 in OA with these associated risk factors should be studied.

While the mechanism(s) by which CCL17 governs OA pain remains to be elucidated, its role in human OA has been recognized as a potential therapeutic target. The human CCL17 inhibitor, GSK3858279, is in phase 1 clinical trials in knee OA (NCT03485365), with phase 1 trials investigating its potential as an analgesic recently completed (NCT04114656). Given that chronic pain is a symptom associated with many inflammatory diseases, the anti-CCL17 inhibitor could be repurposed to provide therapeutic benefit to patients suffering from such conditions.

CCL17 in the central nervous system

Various preclinical models have shown that CCL17 functions in the brain. CCL17 was reported to be a homeostatic and inflammatory neuromodulatory

chemokine whereby it could increase the microglia population while downmodulating the basal synaptic transmission of neurons in the hippocampus.[17] By contrast, CCL17 was found to activate $CCR4^+$ macrophages/microglia in a preclinical model of intracerebral hemorrhage, to reduce the associated brain edema and ameliorate neurological deficits, neuroinflammation and neuronal apoptosis.[42]

CCL17 could play a role in neuropathy. Increased CCL17 expression is seen in the dorsal root ganglia of rats induced with chronic neuropathic pain, and intrathecal administration of CCL17 led to heightened thermal hypersensitivity and pronociception.[43] CCR4 inhibition decreased hypersensitivity and increased opioid analgesia in a preclinical model of diabetic neuropathy.[44] It remains unconfirmed as to whether CCL17 mediates its analgesic activity *via* $CCR4^+$ neurons or other immune cells.[25,38,45,46] Should CCL17 mediate neuropathy in the brain, its therapeutic inhibition could be used to manage pain in more than just inflammatory settings.

Multiple sclerosis

Multiple sclerosis is a chronic inflammatory, autoimmune disease and it is characterized by the degradation of the protective myelin sheath on nerve fibers in the central nervous system, which results in a progressive neurological disability. Experimental autoimmune encephalomyelitis (EAE) is the most studied preclinical multiple sclerosis model and CCL17, as well as CCR4 and GM-CSF, is associated with EAE pathogenesis.[47,48] Indeed, CCL17 upregulates GM-CSF production in $CCR4^+$ DCs, which in turn secrete IL-23 and contribute to EAE development,[49] while another study showed that central nervous system–immigrating DCs secrete high levels of CCL17 in EAE-induced mice, despite IL-23 production being unaffected in CCL17-deficient DCs.[50] Thus, in this model, CCR4 and CCL17 appear to operate at distinct levels in DC-associated immune responses. The former study highlights the non-T–cell biology of CCL17 in EAE, albeit *via* CCR4,[49] although CCL17 is likely to still have a traditional T-cell function(s) in the model. Indeed, CCL17-deficient mice with EAE disease were reported to have an altered T-cell population, with T helper 17 migration into the central nervous system being reduced while Treg expansion was enhanced[50]; because of the involvement of $CCR4^+$ T cells in this model,[50] the efficacy of various CCR4 antagonists has been investigated and, while one has been shown to be efficacious in preclinical trials, efficacy remains to be investigated in patients with multiple sclerosis.[47] Furthermore, given the role of CCL17 in EAE pathogenesis, its targeting is another therapeutic option that merits investigation in multiple sclerosis.

AD and other skin diseases

AD is the most common inflammatory skin disease and is characterized by dry, itchy and chronically inflamed patches of skin. It is a complex disease and often considered to be a type-2 immune response disease. High levels of Th2-associated cytokines, such as IL-4 and IL-13, are found in the serum of patients with AD and these cytokines, in turn, promote the increased production of CCL17 and CCL22 by epidermal keratinocytes, endothelial cells and DCs.[13,51] The elevated platelet population in patients with AD also contributes to the high CCL17 concentration,[52] with the chemokine suggested to be able to recruit functionally impaired $CCR4^+$ Tregs into the skin.[16] CCL17 was reported to be the most reliable AD biomarker and,[53] as it so strongly correlates with AD disease severity, its levels are used to assess therapy efficacy[54]; indeed, CCL17 has been measured commercially for health insurance purposes in Japan since 2008. Elevated CCL17 serum levels have been noted in other skin diseases such as scabies, polymorphic prurigo, cutaneous T-cell lymphoma and pustular dermatosis.[55]

Asthma and other lung diseases

Asthma is a common respiratory disease with its characteristic airway inflammation being driven by type-2 immune pathophysiological responses that are also seen in allergic diseases and AD.[56] CCL17 is elevated in the bronchoalveolar fluid of patients with asthma and is thought to drive the migration of $CCR4^+$ Th2 cells into the lungs.[16] In fact, blocking this migration *via* inhibition of CCL17[57] or CCR4[58,59] has been investigated in a mouse model of allergic airway inflammation and shown to reduce airway hypersensitivity. Interestingly, while *CCL17* gene–deficient mice showed consistent results,[60] for reasons that are not clear, *CCR4* gene–deficient mice showed no apparent phenotype in this model.[61] CCL17 and CCR4 have not been extensively investigated as targets in clinical trials for asthma, except for one phase 1 study for mogamulizumab that was prematurely terminated (NCT01514981). Of note, dupilumab, which targets IL-4Rα, showed clinical efficacy in patients with asthma with reduced CCL17 levels noted,[62] highlighting the potential of targeting CCL17 in asthma.

Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible lung disease, with smoking and long-term exposure to air pollution being associated risk factors.[63] CCL17 expression in COPD was recently

reviewed,[64] and the chemokine was reported to be a predictive biomarker for the rapid decline of lung function (forced expiratory volume in 1 s), with elevated CCL17 levels seen in the epithelial cells and bronchoalveolar lavage fluid of patients with COPD; moreover, high CCL17 serum levels are seen in individuals living in a highly air-polluted environment.[65] However, the exact role of CCL17 in COPD pathogenesis remains unclear. Regardless, a preclinical model of cigarette smoke–induced COPD found that CCL17, secreted by lung epithelial cells, promoted the accumulation of alveolar macrophages in the lung and emphysema,[66] revealing a potential pathogenic role for the chemokine. Moreover, high CCL17 and low CXCL9 serum levels are predictors of declining lung function in chronic bird–related hypersensitivity pneumonitis,[67] with high levels of CCL17 also associated with severe adult and childhood interstitial lung disease.[68]

Eosinophilic disorders

Elevated eosinophil levels in the blood and various tissues can result in a range of disorders of varying severity, and include senile erythroderma, allergic asthma, eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome), acute and chronic eosinophilic pneumonia, lymphoproliferative malignancies such as mycosis fungoides and Sezary syndrome, as well as lymphocytic variant hypereosinophilic syndrome and bullous pemphigoid. The role of CCL17 and its elevated levels in these disorders have been discussed previously.[16] Interestingly, CCL17 was the most highly upregulated gene in GM-CSF–treated mouse eosinophils, which suggests that the GM-CSF/CCL17 pathway may have a role in eosinophilic disorders.[69]

Additional autoimmune/inflammatory diseases

A potential role for CCL17 in additional autoimmune and inflammatory diseases has been identified and it continues to be investigated in other preclinical models. For example, CCL17 was associated with the development of murine colitis,[70] endometriosis[71] and myocardial inflammation.[11] Increased CCL17 levels correlate with the virological response of patients with chronic hepatitis B[72] and CCL17 has been considered to be a potential therapeutic target in cardiac hypertrophy and fibrosis, as well as in many other types of fibrosis.[46] High levels of the chemokine are seen in patients with food-induced anaphylaxis,[73] gastrointestinal food allergies[74] and childhood allergy development,[75] with elevated CCL17 serum levels reported to be a potential diagnostic biomarker for food protein–induced enterocolitis syndrome, which is a non-immunoglobulin E–mediated gut allergic response.[76] Its tear levels have even been suggested to be a diagnostic biomarker for acute and chronic allergic conjunctival disorders,[77] and atopic and vernal keratoconjunctivitis.[78] These studies again highlight the potential for CCL17 to serve at least as a diagnostic biomarker for numerous diseases.

Coronavirus disease 2019

Severe acute respiratory syndrome coronavirus 2 can cause various clinical respiratory symptoms in infected individuals that range in severity, with up to 20% of patients with coronavirus disease 2019 developing severe pneumonia that requires supplemental oxygen or invasive cardiopulmonary support.[79] One study found that high CCL17 expression in the early phase of disease is predictive of a mild to moderate, rather than a severe to critical infection, and that the chemokine could be used as a triage marker during the first day of hospitalization.[79] Interestingly, anti-GM-CSF and anti–GM-CSF receptor mAbs were trialed for early and late stages of coronavirus disease 2019, although their use has not translated into clinical practice.[80]

Cancer

Cancer encompasses a myriad of different diseases affecting all types of tissue, and there is some evidence that CCL17-driven metastasis contributes to the pathogenesis of some cancers. It has been reported that CCL17 promotes bladder cancer cell metastasis,[81] proliferation of cervical cancer cells[82] and mediates human keratinocyte proliferation into cutaneous squamous cell carcinoma.[83] Mechanistically, studies have shown that CCL17-dependent[84] and CCR4-dependent[85] Treg recruitment have been associated with impaired antitumor immunity *via* inhibiting cytotoxic T cells, resulting in tumor growth. These findings highlight the potential use of CCL17/CCR4 axis inhibitors, in conjunction with other treatments (e.g. checkpoint inhibitors), for better clinical outcomes.

CCL17 and Tregs are highly associated with Epstein–Barr virus–positive pyothorax-associated lymphoma cells[86]; further, they are associated with esophageal squamous cell carcinoma.[87] CCL17 is also secreted by multinucleated Reed–Sternberg cells in Hodgkin's lymphoma, and its levels negatively correlate with disease status, treatment response and survival rates for patients.[88] Thus, while cancers are highly heterogeneous, the inhibition of CCL17 and its chemotactic targets may restrict the metastasis and proliferation of some cancer cells.

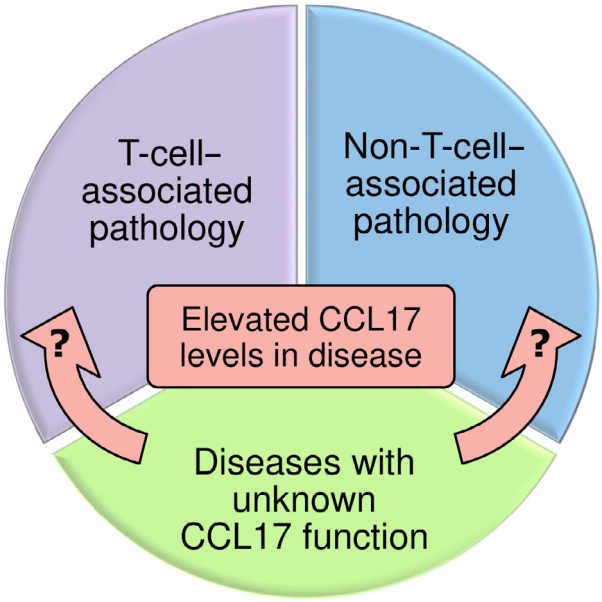

Figure 1. CCL17 is more than a T-cell chemokine. CCL17 is elevated in many autoimmune/inflammatory diseases. CCL17, *via* its cognate receptor, CCR4, is traditionally viewed as a T-cell chemokine with its putative role mainly associated around Th2-driven pathology (e.g. atopic dermatitis and asthma) and Treg-driven pathology (e.g. Hodgkin's lymphoma and cancer metastasis). Recent studies have also implicated CCL17 as having a novel role in non-T-cell–associated pathology; for example, in the pain associated with osteoarthritis and inflammatory arthritis. Given the widespread elevation of CCL17 levels in disease and CCR4 expression in a range of cell types, it is likely that both T-cell–associated and non-T-cell–associated functions will occur (e.g. in eosinophilic disorders and fibrosis). Although CCL17 has been claimed to be associated with many "autoimmune/inflammatory" diseases, many more targeting and mechanistic studies are still needed to determine (i) the relevance of CCL17 to disease pathogenesis, (ii) its mode of action and (iii) whether other unknown stimuli are also involved. CCL17, chemokine (C–C) ligand 17; CCR4, C–C chemokine receptor type 4; Treg, regulatory T cells.

CONCLUDING REMARKS

As indicated earlier, CCL17 has traditionally been viewed as a T-cell chemokine acting *via* its cognate receptor, CCR4, and is often associated with Th2 biology as its expression is elevated in T-cell–associated pathologies (Figure 1), such as AD and asthma, with such expression being upregulated by Th2 cytokines, such as IL-4 and IL-13. Given the wide receptor distribution and its own wide-ranging expression in disease, it is likely that this limited view would be inadequate to explain all CCL17 biology and that there would be other responsive cell types and functions. Indeed, it can be seen from the discussion above that CCL17 can play a role in some T-cell–independent pathologies (Figure 1), such as in OA models, and its deletion/depletion can sometimes have a minor bearing on cell numbers at a site of inflammation, even though it leads to a beneficial outcome. Given the widespread elevation of CCL17 levels in disease and CCR4 expression in a range of cell types, including both T and non-T cells, it is likely that both T-cell–associated and non-T-cell–associated functions will occur, for example, in eosinophilic disorders and fibrosis (Figure 1). Many more targeting and mechanistic studies are obviously needed to determine the relevance of CCL17 to disease pathogenesis and, if so, its mode of action, and whether other unknown stimuli are also involved. As mentioned earlier, in this context there appears to be a GM-CSF/CCL17 pathway acting *in vivo* in both preclinical and clinical studies, again pointing to other CCL17 biology.

As CCL17 shares its receptor with CCL22 and other ligands such as chemokine-like factor 1 (CFKL1),[89] care needs to be exercised in interpreting data resulting from targeting CCR4 directly, that is, in assigning a role for any of these particular ligands. Because there are multiple ligands for CCR4, specific CCL17 blockade could have fewer adverse effects than targeting CCR4 itself, although more research on comparing the biology of the respective components of this system would be informative. A human CCL17 inhibitor is currently being tested in clinical trials for knee OA pain (NCT03485365) and in a battery of evoked pain tests in healthy volunteers (NCT04114656); given the high prevalence of pain globally, this approach could be widely used to treat different types of pain.

This review has outlined some of the new CCL17 biology with implications for its use as a potential diagnostic biomarker and for its therapeutic targeting. Hopefully, further research will be soon forthcoming to answer some of the outstanding questions raised.

ACKNOWLEDGMENTS

KMCL and JAH were supported in part by funding from the University of Melbourne and CSL Limited. AA was supported by funding from the University of Melbourne and the National Health and Medical Research Council (NHMRC). Open access publishing is facilitated by The University of Melbourne, as part of the Wiley – The University of Melbourne agreement via the Council of Australian University Librarians. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

AUTHOR CONTRIBUTIONS

Tanya Lupancu: Conceptualization; writing – original draft; writing – review and editing. **Mahtab Eivazitork:** Conceptualization; writing – original draft; writing – review and editing. **John A Hamilton:** Conceptualization;

supervision; writing – review and editing. **Adrian Achuthan:** Supervision; writing – review and editing. **Kevin Ming-Chin Lee:** Conceptualization; supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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