What does elevated TARC/CCL17 expression tell us about eosinophilic disorders?

Julien Catherine 1,2 · Florence Roufosse 1,2

Received: 9 February 2021 / Accepted: 14 April 2021 / Published online: 19 May 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Eosinophilic disorders encompass a large spectrum of heterogeneous diseases sharing the presence of elevated numbers of eosinophils in blood and/or tissues. Among these disorders, the role of eosinophils can vary widely, ranging from a modest participation in the disease process to the predominant perpetrator of tissue damage. In many cases, eosinophilic expansion is polyclonal, driven by enhanced production of interleukin-5, mainly by type 2 helper cells (Th2 cells) with a possible contribution of type 2 innate lymphoid cells (ILC2s). Among the key steps implicated in the establishment of type 2 immune responses, leukocyte recruitment toward inflamed tissues is particularly relevant. Herein, the contribution of the chemo-attractant molecule thymus and activation-regulated chemokine (TARC/CCL17) to type 2 immunity will be reviewed. The clinical relevance of this chemokine and its target, C-C chemokine receptor 4 (CCR4), will be illustrated in the setting of various eosinophilic disorders. Special emphasis will be put on the potential diagnostic, prognostic, and therapeutic implications related to activation of the TARC/CCL17-CCR4 axis.

Keywords Thymus and activation-regulated chemokine (TARC) · CCL17 · C-C chemokine receptor 4 (CCR4) · Eosinophils · Eosinophilic disorders · Hypereosinophilic syndromes

Abbreviations

AA Allergic asthma  
ABPA Allergic bronchopulmonary aspergillosis  
ADCC Antibody-dependent cell cytotoxicity  
AEC Absolute eosinophil count  
AEP Acute eosinophilic pneumonia  
AITL Angioimmunoblastic T cell lymphoma  
ALI Acute lung injury  
ANCA Anti-neutrophil cytoplasmatic antibody  
ARDS Acute respiratory distress syndrome  
ATLL Adult T cell leukemia/lymphoma  
AUC Area under the curve  
BALF Bronchoalveolar lavage fluid  
BM Bone marrow  
BP Bullous pemphigoid  
CC CC-chemokine  
CCR CC-chemokine receptor  
CEP Chronic eosinophilic pneumonia  
CF Cystic fibrosis  
CLA Cutaneous lymphocyte antigen  
CRSwNP Chronic rhinosinusitis with nasal polyps  
CRTH2 Chemoattractant receptor-homologous molecule expressed on Th2 cells  
CS Corticosteroid  
DC Dendritic cell  
DRESS Drug rash with eosinophilia and systemic symptoms  
EGPA Eosinophilic granulomatosis with polyangiitis  
FEV1 Forced expired volume in one second  
FIP1L1 Fip 1-like 1  
GPCR G protein-coupled receptor  
HC Healthy control  
HDM House dust mite  
HE Hypereosinophilia  
hEoP Human eosinophil progenitor  
HES Hypereosinophilic syndrome

This article is a contribution to the Special issue on: Eosinophils - Guest Editor: Hans-Uwe Simon

Julien Catherine  

julien.catherine@ulb.be

1 Department of Internal Medicine, Hôpital Erasme, 808 Route de Lennik, 1070 Brussels, Belgium  
2 Institute for Medical Immunology, Université Libre de Bruxelles, 6041 Gosselies, Brussels, Belgium
Introduction

A multitude of conditions are associated with the increased presence of eosinophils in blood and/or tissues, ranging from widespread—and generally benign—disorders such as allergic asthma (AA) or atopic dermatitis (AD) to rare but severe diseases such as myeloproliferative hypereosinophilic syndrome variants (M-HES). The relative contribution of eosinophils to pathogenesis of these disorders is variable, partnering with other immune cell types in the setting of complex interactions (e.g., bullous pemphigoid) or acting as key central effector cells contributing to tissue damage like in PDGFRA/FIP1L1-positive M-HES [1, 2]. Among the factors playing a role in the emergence of eosinophilia, interleukin (IL)-5 is a key cytokine with many effects on this cell throughout its life-span [3]. Sources of IL-5 include type 2 helper T cells (Th2 cells), type 2 innate lymphoid cells (ILC2s), or malignantly transformed cells, all of which can potentially be involved in the pathophysiology of eosinophilic inflammation and associated diseases [3].

Thymus and activation-regulated chemokine (TARC), also named CCL17, is a CC-chemokine commonly associated with type 2 immune responses [4]. By binding to C-C chemokine receptor type 4 (CCR4), which is, *inter alia*, expressed by Th2 cells [5], TARC/CCL17 participates in trafficking of Th2 cells in eosinophil-associated disorders including AA and AD and presumably of neoplastic cells in certain T cell lymphomas (e.g., angioimmunoblastic T cell lymphoma (AITL), mycosis fungoides (MF), and Sézary syndrome (SS)) [6]. Thus, elevated serum and/or tissue levels of TARC/CCL17 and cellular CCR4 expression observed in these disorders may serve as biomarkers correlating with disease severity (e.g., AD [7]) and/or be targeted for therapeutic purposes [8].

Herein, current knowledge on the sources, properties, and functions of TARC/CCL17 and its receptor CCR4 will be reviewed extensively, after a brief overview of type 2 immune responses, eosinophil biology, and the definition and classification of eosinophilic disorders. Their participation in eosinophilic inflammation will be illustrated through preclinical models and clinical findings. Finally, we will discuss to which extent the TARC/CCL17-CCR4 axis can serve as a diagnostic or prognostic marker and/or as a therapeutic target in human eosinophilic diseases.

General considerations about type 2 immune responses and eosinophil biology

Type 2 immune cells typically participate in host defense against helminths and are the hallmark of the so-called allergic reaction in which genetically predisposed individuals develop immediate hypersensitivity in response to an antigen, called an allergen, after repeated exposures [9]. As a consequence of decreased epithelial barrier integrity, for example following direct trauma, viral infection, or a genetic defect, the immune system may encounter environmental allergens (e.g., peptides derived from pollen or house dust mite (HDM)) [9]. By secreting alarmins, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), damaged epithelial cells activate ILC2s, the innate non antigen-receptor-expressing counterpart of Th2 [10]. These cells act as a primary source of type 2 cytokines through expression of the transcription factor GATA-3 [10], thereby initiating type 2 responses by recruiting other innate cells (including eosinophils) and promoting Th2 differentiation [11].

Activation and differentiation of naive CD4 T cells into IL-4, IL-5, and IL-13 producing Th2 cells is a key step in the generation of type 2 immune responses. The underlying mechanisms are complex, mainly involving IL-4-dependent activation of signal transducer and activator of transcription (STAT)6 that leads to the expression of GATA-3 which in turn collaborates with STAT5 to drive the expression of IL-4 from the shared *IL4-IL13* gene within the T cell itself [12, 13]. Once activated, Th2 cells migrate to sites of antigen/allergen exposure and...
IL-5 receptor alpha chain (IL-5Rα) progenitors (hEoP) characterized by surface expression of the where common myeloid progenitors give rise to eosinophilic inflammation. In healthy humans, eosinophils are the predominant cell type in humans and mice expressing the IL-5 receptor at high levels, explaining the high specificity of IL-5 for this cell-type. Interleukin-5 forms homodimers that bind to the IL-5Rα chain which is coupled with the signal-transducing common beta chain [3]. Effects of IL-5 include eosinophil development through proliferation, differentiation, and maturation of hEoPs; egress of mature eosinophils from bone marrow; homing and activation in inflamed tissue; and inhibition of peripheral apoptosis [3]. ILC2s represent an important source of IL-5 in homeostatic conditions, supporting for example the colonization of the small intestine and visceral adipose tissue by eosinophils in mice [20, 21]. In pathological situations however, IL-5 derives from Th2 cells and mast cells, in addition to ILC2s [3].

Eosinophil trafficking can be independent of IL-5 as demonstrated by the presence of eosinophils in tissues from IL-5-deficient mice [22]. Several chemokines collectively called eotaxins (eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26)) bind to eosinophil-expressed CCR3 and are key factors in eosinophil chemotaxis, both in homeostatic (CCL11) [23] and inflammatory (CCL24 and CCL26) conditions [24]. Cellular sources of eotaxins include epithelial cells, fibroblasts, smooth muscle cells, endothelial cells, chondrocytes, and macrophages, and their synthesis is dependent on IL-4 and IL-13 [25, 26]. VCAM-1/VLA4 [27], PGD2/chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [28–30], and TSLP/TSLPR [31] interactions are also involved in eosinophil recruitment. The contribution of the TARC/CCL17-CCR4 axis in eosinophil trafficking remains debated, as CCR4 expression by blood and/or lung/bronchoalveolar lavage fluid (BALF) eosinophils has been observed in mice and humans in some [32, 33] but not all studies [34–38].

When engaged in an inflammatory response, eosinophils display a series of effector functions that are largely mediated by pre-formed mediators localized in so-called primary and specific (or crystalloid) granules and in lipid bodies. These mediators, which have been extensively described elsewhere [39], together with reactive oxygen species and IgE antibody-dependent cellular cytotoxicity (ADCC) contribute to host defense against helminths and ectoparasites, even if in vivo data are scarce in humans and divergent in mouse [19]. Furthermore, these effector functions account for eosinophil-mediated cytotoxicity and fibrosis, pro- and anti-inflammatory effects, and antiviral activity to name a few [40] and may cause significant damage in surrounding tissue.

Eosinophilic disease

Eosinophilic disorders encompass a wide range of diseases, from frequent and benign to rare and severe, which are characterized by increased blood and/or tissue eosinophilia associated with variable degrees of eosinophil-mediated damage. Indeed, eosinophil activation and degranulation can result in major, potentially irreversible or lethal organ dysfunction and damage. The archetype of eosinophil-induced toxicity is endomyocardial inflammation favoring formation of mural thrombi and subendocardial fibrosis that may progress to restrictive heart failure. Other deleterious consequences of sustained eosinophilia can occur in all organs including most commonly the skin, lungs, central and peripheral nervous systems, digestive tract, and connective tissue [41].

The definition and classification of eosinophilic disorders were revisited in 2011 by the “International Cooperative Working Group on Eosinophil Disorders” (ICOG-EO), more than 35 years after the first formal elaboration of criteria defining the hypereosinophilic syndrome (HES) [42, 43]. Eosinophilia is defined as an absolute blood eosinophil count (AEC) above \(0.5 \times 10^9/L\), while the term hypereosinophilia (HE) applies when an AEC above \(1.5 \times 10^9/L\) is observed at
least twice, with an interval of at least 1 month. In tissue, HE is present when (1) the percentage of eosinophils in BM exceeds 20% of all nucleated cells and/or (2) a pathologist considers that tissue infiltration by eosinophils is excessive and/or (3) marked deposition of eosinophil granule proteins is found. The term HES is reserved for patients fulfilling the criteria for blood and/or tissue HE and presenting with organ damage and/or dysfunction attributable to eosinophils, after exclusion of other disorders or conditions as potential cause(s) of the observed organ damage [42].

Hyper eosinophilia can be further classified into variants [42]; proliferation of eosinophils may be clonal and is qualified as neoplastic (HE\(_N\)), whereas polyclonal expansion of eosinophils driven by enhanced production of growth factors (mainly IL-5) is qualified as reactive (HE\(_R\)). When the mechanism underlying increased eosinophilopoiesis is unknown and no organ dysfunction or symptoms are present, the term HE of undetermined significance (HE US) applies. Rarely, HE can be detected in several members of a same family and is inherited, defining familial HE.

The first step in the diagnostic approach to eosinophilia or HE is to rule out a reactive/secondary cause [44], such as allergic disease (e.g., severe eosinophilic asthma), parasitosis (e.g., helminths, scabies), adverse drug reactions (e.g., anticonvulsants), and cancer (e.g., certain adenocarcinomas, Hodgkin’s or T cell lymphomas). The second step is to assess for potential eosinophil-induced organ damage. If present, diagnosis of HES must be considered, and further evaluation for HES disease variants is warranted. Neoplastic (HES\(_N\), or primary, clonal, myeloproliferative) HES is associated in approximately 80% of cases with a deletion on chromosome 4q12, creating the Fip 1-like 1 (FIP1L1)/platelet-derived growth factor receptor alpha (PDGFR\(_A\)) fusion gene, which encodes a constitutively active tyrosine kinase (TK) [45]. Reactive (HE\(_R\), or secondary) HES describes situations where reactive HE causes organ damage and dysfunction. Besides classical causes of secondary HE (see above), this entity encompasses lymphocytic variant HES (L-HES) where HE is caused by enhanced IL-5 production by a clonal T cell subset with an abnormal surface phenotype [46]. Finally, the term idiopathic HES (I-HES) is used when the diagnostic work-up fails to identify a known etiology for eosinophilic expansion. This last category accounts for more than half of patients presenting with HES in expert centers [47].

### The biology of thymus and activation-regulated chemokine

#### TARC/CCL17: early discoveries, cellular expression, and mechanisms of synthesis

With the discovery of TARC/CCL17 in 1996, Imai et al. were the first to describe a CC chemokine with selective activity for lymphocytes [48]. Its name reflects the observed constitutive expression in the human thymus and its induction in peripheral blood mononuclear cells (PBMCs) following activation by phytohemagglutinin [48]. One year later, the same team identified CCR4 as the main receptor for TARC/CCL17 and showed that CCR4 mRNA was expressed in CD4+ T cells [49].

Human TARC/CCL17 is an 8-kDa protein composed of 71 amino acids and is encoded on chromosome 16q13 [48, 50]. Murine studies have shown that steady-state TARC/CCL17 synthesis occurs in various tissues including the thymus, lymph nodes (LNs), gut, and bronchi but not in the spleen. The cellular sources of this chemokine were mainly Langerhans cells (LCs) and mature myeloid dendritic cells (DCs) [51]. In humans, monocyte-derived DCs were shown to synthetize TARC/CCL17 in response to IL-3 and tumor necrosis factor alpha (TNF-\(\alpha\)) in presence of IL-4 in in vitro cultures [5]. Subsequently, several immune and non-immune cellular sources of TARC/CCL17 were identified, as detailed in Table 1.

Molecular mechanisms underlying TARC/CCL17 synthesis and secretion are variable depending on the nature of the cell and the stimuli. In immune cells, IL-4 stimulates TARC/CCL17 synthesis, synergizing with other cytokines depending on the cell type [5, 52–54]. STAT6 activation is a key step in IL-4-induced TARC/CCL17 synthesis by binding directly to the CCL17 gene promoter via two binding sites (Fig. 1) [55]. In keratinocytes and bronchial and alveolar epithelial cells, TARC/CCL17 synthesis is triggered by TNF-\(\alpha\) and interferon (IFN)-\(\gamma\) that act synergistically in a nuclear factor-kappa B (NFkB)-dependent manner [56–58], consistent with the presence of a NFkB binding site in the CCL17 promoter [59]. The effect of IL-4 varies, with an inhibitory effect observed in keratinocytes [56, 60] while a co-stimulatory effect applies to other cell types (Table 1).

#### TARC/CCL17 selectively binds to CCR4

CCR4 belongs to the G protein-coupled receptor (GPCR) family and is thus composed of seven transmembrane domains [61]. In addition to TARC/CCL17, CCR4 binds macrophage-derived chemokine (MDC/CCL22) which shares 37% homology in its amino acid sequence [6]. MDC/CCL22 is also expressed in the human thymus [62] and produced by DC, macrophages, and monocytes [63–65]. MDC/CCL22 exhibits 2- to 3-times higher affinity for CCR4 compared with TARC/CCL17 [62] and is more potent in promoting integrin-dependent arrest of lymphocytes on VCAM-1 [66] as well as inducing CCR4 desensitization and internalization [67]. These differences may be explained by different CCR4 conformations. In human T cells, the major R1 form binds both chemokines while the minor R2 forms only bind MDC/CCL22. When all R1 receptors are occupied, MDC/CCL22 is still able to increase chemotaxis through R2 receptors whereas an additive effect of TARC/CCL17 is not possible.

---

**Semin Immunopathol (2021) 43:439–458**

---

**Springer**
| Cellular sources of TARC/CCL17 | Species | Inducer(s) | Inhibitors(s) | Potential intracellular pathways involved | Ref(s) |
|-------------------------------|---------|------------|---------------|------------------------------------------|--------|
| Monocytes                     | Human   | IL-4, IL-3, GM-CSF | IFN-γ, IL-10 | JAK1/3, AK3, STAT6, JMYD3, IRF4 | [5, 52, 53] |
| Monocyte-derived DCs          | Human   | IL-4, GM-CSF | No effect of IFN-γ | | [5] |
| Macrophages                   | Mouse   | IL-4, GM-CSF | IFN-γ | | [52, 53, 158] |
| M2 macrophages                | Human   | IL-4, IL-13, RANK engagement | Pan-PI3K inhibitor, no effect of glucocorticoids | PI3K | [103a, 159] |
| Myeloid DCs                   | Human, CD11c+ DCs | TSLP, TSLP + RANK or CD40 engagement | / | / | [160, 161] |
| Mouse, CD11c+ DCs             | Mouse   | TSLP | / | / | [162] |
| Langerhans cells (skin)       | Mouse   | TNF-α, IL-4, IL-13 | IFN-γ, GM-CSF | | [164] |
| Monocyte-derived LCs          | Human, AD patients | S. aureus extract (PGN) | Histamine H4 receptor antagonist | p38 MAPK | [165] |
| Eosinophils                   | Human, allergic volunteers | IL-4, IL-4+TNFα | / | / | [32] |
| CD3+ T cells                  | Human, HC | IL-4 | / | / | [171] |
| CD4+CD45RA+ T cells           | Human, AA patients | PBMC stimulation with Der allergen | Anti-CD80 + CD86 Abs | / | [104] |
| Keratinocytes                 | Human   | TNF-α + IFN-γ<sup>a</sup> | IL-4, IL-13, TGF-β, Casuamin, Spinasterol Glc, Allopurinol, Roxithromycin | p38 MAPK, Raf1, JAK2, STAT1, NFκB | [56, 60, 166–171] |
| Bronchial epithelial cells    | Human, Mouse | HDM extract, IL-22 | / | / | STAT3, ERK, AKT | [79] |
|                             | Human   | TNF-α + IFN-γ +/- IL-1α<sup>b</sup> | Glucocorticoids, Long-acting β-2 adrenergic agonist | NFκB | [172] |
|                             | Human   | TNF-α + IL-4 + IFN-γ<sup>a</sup> | IL-4 alone: weak or no effect | NFκB | [57, 58, 173] |
|                             | Human   | Der p alone | / | / | ADAM-dependent EGFR phosphorylation, | [101] |
|                             | Human   | Der p + IL-4 + TGF-β (highest response) | Der p + IL-4 + TGF-β | / | p38 MAPK, ERK1/2, NFκB | [57, 58, 173] |
|                             | Human   | IL-4 alone: no effect | / | / | / | [173] |
|                             | Human   | TLR3 ligand poly(I:C) | / | / | / | [174] |
|                             | Human   | TWEAK + TGF-β<sup>c</sup> during EMT | / | / | / | [175] |
|                             | Human   | TNF-α or IL-1α alone | Glucocorticoids | NFκB, STAT6 | [57, 58, 176] |
|                             | Human   | TNF-α or IL-1α or IFN-γ + IL-4 or IL-13<sup>b</sup> | RSV + IL-4 or IL-13<sup>b</sup> | / | / | [177] |
|                             | Human   | IL-4/IL-13 alone: no effect | / | / | / | [178] |
|                             | Human   | TNF-α + IL-4 or IL-13 | / | / | / | [179] |
|                             | Human   | IL-4 or IL-13 + TNF-α | β-adrenergic agonist (isoprotereno), no effect of glucocorticoids | p38 MAPK, NFκB | [166, 179] |
|                             | Human   | IL-4/IL-13 alone: no effect | No effect of glucocorticoids | / | / | [166, 179] |

Abs antibodies, AD atopic dermatitis, ADAM a disintegrin and metalloproteinase, CD40L, CD40 ligand, DC dendritic cells, Der f/p dermatophagoides farinae/pteronyssinus, dsRNA double-stranded ribonucleic acid, EGFR epidermal growth factor receptor, EMT epithelialmesenchymal transition, ERK extracellular signal regulated kinase, GITR(L) glucocorticoid-induced TNFR-related protein (ligand), GM-CSF granulocyte monocyte colony stimulating factor, HC healthy controls, HDM house dust mite, IFN interferon, IL interleukin, IRF interferon regulatory factor, JMYD Junonij C domain-containing proteins, JNK Janus kinase, LC Langerhans cell, LPS lipopolysaccharide, MAPK mitogen-activated protein kinase, MEK mitogen-activated protein/extracellular signal-regulated kinase kinase, NFκB nuclear factor-kappa B, PGN peptidoglycans, P38K phosphoinositide 3-kinase, PBMC peripheral blood mononuclear cell, RANK(L) receptor activator of nuclear factor kappa-B (ligand), RSV respiratory syncytial virus, STAT signal transducers and activators of transcription, TGF transforming growth factor, TLR toll-like receptor, TNF tumor necrosis factor, TSLP thymic stromal lymphopoietin, TWEAK tumor necrosis factor (TNF)-like weak inducer of apoptosis

<sup>a</sup> In this study, macrophages demonstrated a partial M2 phenotype

<sup>b</sup> A synergistic effect appears when cells are co-stimulated with these agents

<sup>c</sup> A synthetic analog of viral dsRNA
Furthermore, GPCR-induced chemoattraction by MDC/CCL22 of in vitro differentiated murine Th2 cells was shown to rely not only on the phosphatidylinositol 3-kinase (PI3K) signaling pathway (shared with TARC/CCL17) but also on beta-arrestin-2, enhancing chemotaxis [69]. Whether the activation of this pathway by MDC/CCL22 is linked to a distinct CCR4 conformation is not known.

Functional characterization of CCR4-expressing CD4+ T cells supports their Th2 differentiation as they spontaneously synthesize IL-4 and IL-5 but no IFN-γ in in vitro cultures [5]. These early discoveries suggested a potential role of TARC/CCL17 and CCR4-expressing cells in type 2 immune responses as discussed below. Besides Th2 cells, several other cell types involved in type 2 immune responses express...
CCR4, including ILC2s [70]. Other populations reported to be CCR4-positive are listed in Table 2.

**TARC and its relevance in eosinophilic diseases**

Several studies have shown that TARC/CCL17 may be increased in serum and/or tissues in various eosinophilic conditions. These findings are summarized in Table 3 and described in more detail below.

**Skin disorders**

**Atopic dermatitis** (AD) is a chronic inflammatory disease characterized by upregulation of Th2 and Th22 cytokines in the acute phase, while a Th1 and Th17 profile has been demonstrated by gene expression studies in chronic lesions [71]. A type 2 immune response is central in the pathogenesis of AD, with production of allergen-specific IgE-type antibodies [71]. Eosinophilia is common in blood and skin in this disorder, but is not likely to play a central role in established lesions, as suggested by the lack of clear-cut efficacy of the anti-IL-5 monoclonal antibody (MoAb) mepolizumab in clinical trials [72, 73].

TARC/CCL17 is expressed in both acute and chronic lesions of AD by epidermal keratinocytes, dermal-infiltrating cells (CD3+ T cells and CD1a+ DC), and endothelial cells, while it is absent in normal skin [74]. Consequently, higher levels of serum (s)TARC/CCL17 are observed in AD compared to healthy controls (HC) [74]. Their levels correlate with AEC and weakly with sIL-2R-alpha (sCD25) levels, a known biomarker of T cell activation in vivo [75, 76]. T cells expressing CCR4 are detectable in lesional skin at the dermoeidermal junction, and the proportion of circulating CD4+CD45RO+ cells expressing CCR4 is higher in patients with AD compared to HC [75]. Of note, in AD, most of the circulating CCR4+ T cells were also positive for cutaneous lymphocyte antigen (CLA) in two other studies [77, 78].

The contribution of the TARC/CCL17-CCR4 axis to AD pathogenesis involves several mechanisms. We previously mentioned the importance of TNF-α and IFN-γ in TARC/CCL17 synthesis by the keratinocyte cell line HaCaT and its repression by IL-4. Furthermore, in vitro cultured peripheral T cells from HC produce IL-22, TNF-α, and IFN-γ in response to HDM extracts, whereas HaCaT cells upregulate IL-22/RA and sTARC/CCL17 at their surface. Activation of the IL-22/IL-22Rx axis leads to production of TARC/CCL17, IL-1α, and IL-6 by HaCaT cells and recruitment of CCR4+ T cells [79]. Finally, regulatory CD4+CD25+ T cells (Treg) are known to express CCR4 and display higher expression levels in patients with severe AD compared to HC combined with a reduced ability to secrete transforming growth factor (TGF)-β and IL-10 and to suppress autologous effector T cells in vitro, indicating the probable recruitment of functionally impaired Tregs into AD skin [80].

**Drug rash with eosinophilia and systemic symptoms** (DRESS) is a severe drug reaction associating a disseminated rash, fever, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and organ dysfunction [81]. Serum TARC/CCL17 levels may be extremely elevated in this disorder, and CD11c+ DC have been shown to be the main source in lesional skin [82]. The level of sTARC/CCL17 correlates positively with the severity of skin manifestations as well as AEC and sCD25 [82] and is significantly higher in patients with demonstrated HHV-6 reactivation [83], although the causal link between viral reactivation and TARC/CCL17 over-expression remains elusive. Some argue that increased TARC/CCL17 could attract Tregs and alter antiviral responses leading to HHV-6 reactivation or, alternatively, TARC/CCL17 could directly induce HHV-6 activation through the chemokine receptor homologues of HHV-6 [83, 84].

**Bullous pemphigoid** (BP) is an autoimmune blistering disease characterized by autoantibodies targeting hemidesmosomes and is often accompanied by blood eosinophilia, elevated serum IgE levels, and a dermal infiltrate mainly composed of lymphocytes and eosinophils [1]. Several lymphocyte subsets seem implicated in BP including Th2 and Th17 cells [1]. Eosinophils are thought to play a pathogenic role since their degranulation is induced by FcεRI engagement by anti-basement membrane IgE, leading to blister formation in a humanized mouse model of BP [85]. Elevated TARC/CCL17 levels have been found in blister fluid and serum from patients with BP, and this chemokine was detected by immunohistochemistry (IHC) in basal epidermal keratinocytes from lesional skin of BP patients while CCR4 was expressed by dermal CD4+ and peripheral blood CD4+CD45RO+ T cells [86].

---

**Table 2** Human cells and tissues with demonstrated CCR4 expression

| Cells expressing CCR4 in humans | Reference(s) |
|---------------------------------|--------------|
| Type 2 helper cells (Th2)       | [5, 180, 181]|
| CLA+ T cells                    | [77, 182]    |
| Type 2 polarized CD8+ T cells   | [183, 184]   |
| Regulatory T cells (Tregs)      | [80, 185]    |
| T helper 17 cells (Th17)        | [186]        |
| T helper 22 cells (Th22)        | [187]        |
| Type 2 innate lymphoid cells    | [70, 188, 189]|
| Airway eosinophils (AA patients)| [32]         |
| Airway mast cells (AA patients) | [190]        |
| Plasmacytoid DCs (AA patients)  | [191]        |
| Conventional DCs (AA patients)  | [192]        |
| Airway epithelial cells (BEAS-2B, A549 cell lines) | [193] |
### Table 3  Eosinophilic disorders with enhanced TARC/CCL17 production

| Disorder                          | Site/magnitude of sTARC/CCL17 increase | Principal cellular source of TARC/CCL17 | Correlation(s) of sTARC with other biomarkers/clinical features | Potential clinical implications | Refs |
|-----------------------------------|---------------------------------------|----------------------------------------|---------------------------------------------------------------|---------------------------------|------|
| Atopic dermatitis                 | Skin, Serum Median 1733 pg/mL (IQR 696-4742) | Epidermal keratinocytes, Dermal fibroblasts, Endothelial cells, Langerhans cells, CD1a+ DCs | (+) Score AD Index (SCORAD), (+) Six sign AD (SASSAD), (+) Blood eosinophils, (+) Serum soluble E-selectin, (+) sCD25 | Assessment and monitoring of disease severity | [7, 56, 74, 165] |
| DRESS                             | Skin, Serum Mean 31,259 pg/ml (SEM 6374) | CD11c+ DCs | (+) Blood eosinophils, (+) sCD25, (+) Skin lesions severity | Differentiation with other drug-induced skin reactions (SJS, maculopapular erythema) Association with higher sTARC/CCL17 and HHV-6 reactivation | [82, 83] |
| Bullous pemphigoid                 | Skin, Serum Mean 1151 pg/mL (range, 91-3981) | Epidermal keratinocytes | (+) Blood eosinophils, (+) BP Disease Area Index score, (+) Uricaria/erythema scores | Disease activity monitoring (earlier elevation than anti-BPI80 autoantibodies) | [86, 138] |
| Senile erythroderma                | Serum, Median 6872 pg/ml (IQR: 4303-25,683) (idiopathic group) | Not assessed | (+) Serum IgE | sTARC/IgE ratio higher in chronic idiopathic erythroderma than in AD in elderly > differential diagnosis | [88, 89] |
| Allergic asthma                   | Bronchial epithelium BALF, Sputum, Serum Mean 271 pg/mL (range, 50-1000 pg/mL) | Bronchial epithelial cells, M2 macrophages, CD11c+ DCs, CD4+CD45RA+ T cells, Eosinophils | (+) Serum MDC & serum eotaxin, (+) Serum IgE (inconstant finding), (-) PEFR in children with exacerbated AA | Potential therapeutic target through inhibition of Th2 cells and potentially ILC2 accumulation in airways Combination of sTARC, sCCL26, FeNO and AEC identifies type 2-high asthmatic population* (PPV 100%, NPV 87%) | [32, 194–197] |
| EGPA                               | Sinus, Serum Mean 1122 pg/mL (SEM ±422.7) | Not assessed (perivascular inflammatory infiltrate) | (+) Serum IgE, (+) Blood eosinophils | Correlates with disease severity but does not predict relapse | [115, 116] |
| ABPA (associated with CF)          | Serum, Median 589 pg/mL (IQR 463-673) | Not assessed | (+) A. fumigatus-specific IgE, (+) Recombinant A. fumigatus allergen | Differentiation btw ABPA and aspergillus sensitization or colonization in CF Earlier detection of disease onset compared with total IgE kinetics Highly sensitive and specific for AEP among patients with ALI or ARDS | [112, 140] |
| Acute eosinophilic pneumonia       | BALF, Serum, Median 17,907 pg/mL (range 15,533-32,731) | Alveolar DCs, Macrophages | (+) TARC/CCL17 in BALF, (+) TARC/CCL17 in BALF and CCR4+ CD4 T cells in BALF | Highly sensitive and specific for AEP among patients with ALI or ARDS | [119-122] |
| Mycosis fungoides and Sézary syndrome | Skin, Serum, Mean 2889 pg/mL (SEM 725.5) (MF, all stages included) | Keratinocytes (MF) | (+) LDH (MF), (+) Serum IgE (MF), (+) Serum sCD25 (MF), (+) MDC (MF) | Assessment of disease progression in MF Targeted treatment: Mogamulizumab, approved for relapsed/refractory MF or SS (improves PFS compared to vorinostat) Targeted treatment: Mogamulizumab approved for use as add-on to intensive chemotherapy (improves PFS and OS) | [127, 154, 198] |
| Adult T cell leukemia--lymphoma    | Skin, Serum | Not assessed | – | High (> 285 pg/mL) sTARC/CCL17 associated with unfavorable prognosis Targeted treatment: Mogamulizumab approved for use as add-on to intensive chemotherapy (improves PFS and OS) | [131, 142, 156, 199] |
| L-HES                              | Skin, Serum | DCs (in vitro) | No correlation with blood CD3+ CD4+ T cell count | Markedly elevated sTARC/CCL17 suggestive of L-HES among patients with F/P HES | [136, 137, 143] |
Table 3 (continued)

| Disorder                        | Potential clinical implications | Refs |
|---------------------------------|---------------------------------|------|
| **Allergic asthma**             |                                 |      |
| **AA**                          |                                 |      |
| **ABPA**                        |                                 |      |
| **AD**                          |                                 |      |
| **AEC**                         |                                 |      |
| **AEP**                         |                                 |      |
| **ALI**                         |                                 |      |
| **ARDS**                        |                                 |      |
| **BALF**                        |                                 |      |
| **BTW**                         |                                 |      |
| **CCL26**                       |                                 |      |
| **CC chemokine 6**              |                                 |      |
| **CC chemokine receptor 4**     |                                 |      |
| **CF**                          |                                 |      |
| **DC**                          |                                 |      |
| **DRESS**                       |                                 |      |
| **EGPA**                        |                                 |      |
| **FeNO**                        |                                 |      |
| **FEV1**                        |                                 |      |
| **F/P**                         |                                 |      |
| **Fip 1-like 1**                |                                 |      |
| **PDGFRA**                      |                                 |      |
| **IQR**                         |                                 |      |
| **IgE**                         |                                 |      |
| **ILC2s**                       |                                 |      |
| **L-HES**                       |                                 |      |
| **MDC**                         |                                 |      |
| **MF**                          |                                 |      |
| **OCS**                         |                                 |      |
| **OS**                          |                                 |      |
| **Ps**                          |                                 |      |
| **PFS**                         |                                 |      |
| **SEM**                         |                                 |      |
| **SJS**                         |                                 |      |
| **SS**                          |                                 |      |
| **Th2**                         |                                 |      |
| **Th2-regulated chemokine**     |                                 |      |
| **T2**                          |                                 |      |
| **TARC/CCL17**                  |                                 |      |
| **T-cell**                      |                                 |      |
| **T-helper 2**                  |                                 |      |
| **Th2**                         |                                 |      |
| **Th2 cells**                   |                                 |      |
| **Th2 cytokines**               |                                 |      |
| **Th2 myeloid cells**           |                                 |      |
| **Th2 subset**                  |                                 |      |
| **Th2-mediated**                |                                 |      |
| **Th2-mediated disorders**      |                                 |      |
| **Th2-mediated immune response**|                                 |      |
| **Th2 cells**                   |                                 |      |
| **Th2 subset**                  |                                 |      |
| **Th2 mediator**                |                                 |      |
| **Th2 regulatory cells**        |                                 |      |
| **Th2 skewing**                 |                                 |      |
| **Th22**                        |                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22-mediated**               |                                 |      |
| **Th22-mediated disorders**     |                                 |      |
| **Th22-skewed**                 |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
| **Th22 mediator**               |                                 |      |
| **Th22 regulatory cells**       |                                 |      |
| **Th22 skewing**                |                                 |      |
| **Th22-mediated immune response**|                                 |      |
| **Th22 cells**                  |                                 |      |
| **Th22 subset**                 |                                 |      |
[102], M2 macrophages [103], and CD4+CD45RA+ T cells [104]. Eosinophils themselves are a potential source of TARC/CCL17 and MDC/CCL22 as demonstrated in a mouse model of allergic airway inflammation [105] and after in vitro stimulation with different cytokines in humans [106]. Altogether, these data indicate that TARC/CCL17 may contribute to effector T cell chemotaxis to lungs in asthma. Although it has been shown that CCR4+ T cells are the main source of type 2 cytokines in asthmatic patients [98], the functional relevance of the TARC/CCL17-CCR4 axis in AA remains to be elucidated, as targeting this pathway in animal models has produced conflicting results with regard to the consequences on airway hyperresponsiveness and airway inflammation [102, 107–110].

Other airway disorders Patients with allergic rhinitis and chronic rhinosinusitis with nasal polyps (CRSwNP) were reported to have higher TARC/CCL17 levels in nasal secretions than patients with non-allergic, non-infectious rhinitis and chronic rhinosinusitis without nasal polyps, and higher sTARC/CCL17 than HC [111]. Elevated sTARC/CCL17 levels have also been observed in patients with allergic bronchopulmonary aspergillosis (ABPA) both in the setting of cystic fibrosis (CF) and AA [112]. In patients with CF, a positive correlation was observed with A. fumigatus-specific IgE [112].

Eosinophilic granulomatosis with polyangitis (EGPA, formerly Churg-Strauss syndrome) is a rare granulomatous, eosinophil-rich, necrotizing vasculitis affecting small- and medium-sized vessels and associated with late-onset asthma and eosinophilia [113]. In 30–40% of cases, EGPA is associated with antineutrophil-cytoplasmic-antibodies (ANCAs) [114]. The pathogenesis of EGPA is complex, involving type 2 immunity, B cell activation with antibody production, and Th17 cells [114]. Patients with EGPA often have a history of allergic disease and high serum IgE levels [114]. TARC/CCL17 is expressed in active EGPA lesions in association with eosinophilic infiltrates, colocalizes with CRTH2+ T cells, and elevated serum levels have been reported in several studies [115–117]. sTARC/CCL17 has been shown to correlate with disease activity, AEC, and serum IgE levels in this disease [115].

Acute and chronic eosinophilic pneumonia (AEP and CEP) are characterized by eosinophilic infiltration of the lung parenchyma, and the former may progress to an acute respiratory distress syndrome in some cases [118]. Blood eosinophil counts are generally within normal ranges at diagnosis of AEP while they are increased in 80% of patients with CEP [118]. Elevated levels of type 2 cytokines and TARC/CCL17 in BALF have been reported in both disorders [119]. There was a tendency toward higher TARC/CCL17 levels in AEP, and a positive correlation was observed with IL-5 and IL-13 in this disorder [119]. Similarly, sTARC/CCL17 levels were significantly higher in AEP than in sarcoidosis, hypersensitivity pneumonitis, and interstitial pulmonary fibrosis [119]. A challenge with the suspected trigger of AEP in two patients was followed by a rise in sTARC/CCL17 within 16 h after provocation [120]. Cellular sources of TARC/CCL17 identified in AEP comprise alveolar DC and macrophages [121]. CCR4-positive CD4+ T cells were significantly higher in BALF than in blood in patients with AEP and CEP and were not observed in BALF from HC or patients with sarcoidosis [122]; their numbers correlated positively with BALF TARC/CCL17, MDC/CCL22, and IL-5 [122]. Ultimately, transendothelial migration of eosinophils in response to BALF from patients with AEP, assessed in vitro using human pulmonary microvascular cells, was not abrogated by a CCR4 antagonist in vitro [123]. Together, these findings highlight the increased presence and probable role of the CCR4/CCL17 axis in T cell chemotaxis to the lungs in AEP, but other factors may contribute to eosinophil accumulation.

Lymphoproliferative malignancies

Mycosis fungoides (MF) and Sezary syndrome (SS) belong to the spectrum of cutaneous T cell lymphoma and are characterized by clonal proliferation of mature T cells in the skin [124]. Disease course in MF is progressive while SS is more aggressive and generally combines circulating neoplastic T cells, erythroderma, and lymphadenopathy [125]. As disease progresses, the cytokine profile in MF evolves from type 1 to type 2, while SS typically displays only a type 2 profile where cytokine levels correlate with blood eosinophilia and serum IgE [125]. The atypical lymphoid cells that characterize this disease spectrum have hyperchromatic cerebriform nuclei, they can be detected in peripheral blood, and their distribution within tissue depends on the disease stage [125, 126]. These cells typically express CLA and CCR4 at their surface, while TARC/CCL17 is present within keratinocytes in affected skin [74]. sTARC/CCL17 levels are elevated in all disease stages but are significantly higher in advanced (tumor) stage MF and in SS [127, 128]. Expression of CCR4 may be observed in other T cell malignancies as well, such as angioimmunoblastic T cell lymphoma (AITL), unspecified peripheral T cell lymphoma (PTCL-U), and adult T cell leukemia/lymphoma (ATLL) [129]. TARC/CCL17 was detected by IHC in lymph nodes from patients with AITL and PTCL-U with in cells with dendritic morphology, and its expression level correlated with eosinophilic infiltration in lymphomatous tissue [130]. Elevated TARC/CCL17, MDC/CCL22, and CCR4 mRNA expression was reported in skin from patients with ATLL compared with HC [131]. In vitro chemotaxis assays showing that the CCR4+ malignant T cells isolated from peripheral blood...
of ATL patients respond strongly to TARC/CCL17 and MDC/CCL22 indicate that this axis plays a functional role in pathogenesis of this disorder [131].

**Hypereosinophilic syndromes**

**Lymphocytic variant HES** (L-HES) is an indolent T cell lymphoproliferative disorder in which the clonal cells display an abnormal surface phenotype (most often CD3+CD4+TCRα/β) and produce type 2 cytokines including IL-5 [132], explaining its classification as HESR. Common clinical manifestations include skin lesions, angioedema, lymphadenopathy, and rheumatological involvement [133, 134]. In a study investigating chemokine receptor expression on these naturally occurring cells, our group showed that CD3+CD4+ cells expressed CCR5, CXCR4, and CCR4, although the latter was observed only when cells were left in autologous serum-free milieu suggesting that CCR4 was internalized in vivo [135]. Measurement of its ligands TARC/CCL17 and MDC/CCL22 in serum from subjects with CD3+CD4+ L-HES confirmed that sTARC/CCL17, but not sMDC/CCL22, levels were markedly elevated compared to controls, a finding that was subsequently observed in L-HES patients with other phenotypically aberrant T cell subsets as well [135, 136]. Cellular sources of TARC/CCL17 have not yet been explored in vivo, but it was shown in vitro that IL-4 issued from CD3+CD4+ cells can stimulate its production by DC, but not by eosinophils or T cells [135]. A subset of patients with CD3+CD4+ L-HES present clinically with Gleich’s syndrome, also known as episodic angioedema with eosinophilia. One study has shown that serum IL-5 and sTARC/CCL17 peak prior to blood eosinophilia and symptoms in such patients, suggesting an early role for this chemokine in the cascade of events leading to a flare [95].

Besides those with well-documented L-HES, a subset of patients with I-HES have higher sTARC/CCL17 levels than HC. One study showed that PBMC isolated from these patients display some degree of spontaneous IL-5 production in vitro, contrasting with I-HES patients with normal sTARC/CCL17 levels [136]. The proportion of I-HES patients with above-normal sTARC/CCL17 levels reached 36% in a large retrospective multicentric study, although the geometric mean was lower than in patients with L-HES (3406 vs 12,979 pg/mL respectively, p=0.02) [137].

**Clinical implications**

Activation of the TARC/CCL17-CCR4 axis, as reflected by elevated sTARC/CCL17 levels, may provide clues to the differential diagnosis of certain inflammatory disorders, predict disease severity, and/or help monitor disease activity (Table 3). In certain instances, this axis plays a pathogenic role, either because TARC/CCL17 is a key factor eliciting inflammation or because aberrant cells that drive pathogenesis express CCR4, and therefore represents a potential therapeutic target.

**TARC as a biomarker for diagnosis, disease activity, and prediction of disease severity and treatment responses**

**Atopic dermatitis** In AD patients, an early study showed that sTARC/CCL17 correlated with disease activity (assessed by Scoring AD index, SCORAD) and AEC [75]. A prospective study conducted on a large cohort (n=320) of adults with AD highlighted the accuracy of sTARC/CCL17 to monitor disease severity given the positive relationship between this chemokine and clinical skin scores [7]. Moreover, elevated sTARC/CCL17 at presentation could also predict a more severe course, although this remains to be firmly established given some observed heterogeneity in results so far [7].

**DRESS** In patients with severe drug reactions, elevated sTARC/CCL17 has been shown to be a discriminating factor for diagnosis of DRESS rather than Steven-Johnson syndrome and maculopapular erythema [83]. In patients with DRESS, sTARC/CCL17 correlates with the severity of skin manifestations at onset and decreases together with skin healing and normalization of serum IL-5 [82].

**Bullous pemphigoid** A positive correlation has been observed between AEC and sTARC/CCL17 as well as disease activity, indirectly suggesting that sTARC/CCL17 could also correlate with disease activity [86]. In this line, sTARC/CCL17 levels were shown to correlate with the BP Disease Area Index score as well as urticaria/erythema scores in a series of 20 BP patients [138]. Serum TARC/CCL17 may actually be a better marker of disease activity than anti-BP180 autoantibodies, as fluctuations occurred earlier in patients experiencing disease flares in a recent study [138].

**Senile erythroderma** Although a positive correlation has been observed between IgE and sTARC/CCL17 in patients with both idiopathic and secondary senile erythroderma [88], sTARC/CCL17 was more markedly elevated in patients with chronic idiopathic erythroderma (predominantly male) in one study, leading the authors to propose the use of a sTARC/IgE ratio to distinguish this patient sub-group from elderly patients with AD, showing a sensitivity of 80% and a specificity of 95% when the ratio is superior to 7.24 [89].
**Chronic obstructive pulmonary disease** TARC/CCL17 was an independent predictive biomarker for the rapid decline in forced expiratory volume in one second (FEV$_1$) in stable patients with COPD [139].

**EGPA** sTARC/CCL17 is elevated in EGPA and correlates with disease activity [115]. Unfortunately, neither eotaxin-3/CCL26 nor TARC/CCL17 had sufficient accuracy for relapse-prediction in previously treated patients [116]. In addition, neither chemokine was useful to distinguish patients with ANCA-negative EGPA from those with HES presenting with a history of asthma and sinusitis [117].

**ABPA** sTARC/CCL17 was shown to be more reliable than total IgE and *A. fumigatus*-specific IgE in serum for the diagnosis of ABPA in patients with CF and helped discriminate this condition from simple colonization or sensitization to *A. fumigatus* where levels are normal [112]. In addition, the rise in sTARC/CCL17 precedes that of IgE during disease development, offering the potential for early detection and management of this debilitating condition [140]. Higher sTARC/CCL17 levels may predict more severe disease as the levels of this chemokine correlated negatively with lung function in CF patients with ABPA [112].

**Acute eosinophilic pneumonia** In patients with acute lung injury (ALI), sTARC/CCL17 levels accurately differentiate patients with severe forms of AEP from those with acute interstitial pneumonia, pneumonia-associated ALI/ARDS, and patients with alveolar hemorrhage. In fact, among several candidate biomarkers (including eotaxin-1/CCL11, Krebs von den Lungen-6 (KL-6) and surfactant protein-D), sTARC/CCL17 had the largest AUC (1.00, 95% CI 1.00 to 1.00) with a concentration threshold from 6259 to 7040 pg/mL [120]. Furthermore, sTARC/CCL17 levels correlated with those in BALF during active disease and decreased in parallel with regression of symptoms [120].

**T cell lymphoma** In MF and SS, CCR4$^+$ cell numbers increase in parallel with disease progression [128], and higher expression of CCR3 and CCR4 by lymphomatous cells in skin samples is associated with poor survival [141]. In MF, sTARC/CCL17 were significantly higher in tumor stage than in patch or plaque stage [127]. CCR4 expression by malignant cells is also associated with a poor prognosis in patients with ATLL and PTCL-U [129, 142].

**Hypereosinophilic syndrome** In patients presenting with persistent unexplained HE, markedly elevated sTARC/CCL17 levels are associated with L-HES whereas normal values are observed in patients with no evidence for underlying Th2-driven pathogenesis [136]. In a recent study on a large cohort of HES patients, our group determined that a threshold value of 3000 pg/ml should raise suspicion of L-HES [143] although similarly elevated levels were also observed in patients with I-HES presenting clinically as eosinophilic dermatitis. A rise in sTARC/CCL17 could also be an early marker heralding a disease flare in patients with episodic angioedema with eosinophilia associated with CD3 CD4$^+$ T cells [95].

Furthermore, sTARC/CCL17 levels may help predict treatment responses in HES. In a large multi-center retrospective study, the geometric mean sTARC/CCL17 level was significantly higher in CS-responsive patients compared to non-responders (979 vs 242 pg/mL, $p=0.01$) [137]. In another study evaluating the efficacy of mepolizumab in patients with FIP1L1-PDGFRα-negative HES, a suboptimal hematological response to mepolizumab was observed in patients with elevated sTARC/CCL17 levels, whether or not they had L-HES [144].

**The TARC/CCL17-CCR4 pathway as a therapeutic target in eosinophil-associated disorders**

To date, two main approaches have been employed to target CCR4-positive cells and/or antagonize the actions of TARC/CCL17 and MDC/CCL22. The first one is represented by a MoAb specifically targeting the extracellular portion of CCR4, namely, mogamulizumab (KW0761). It is a defucosylated humanized IgG1 kappa MoAb that destroys CCR4-positive cells through ADCC and is approved for the treatment of certain T cell neoplasms [8, 145]. Of note, mogamulizumab administration can be associated with occurrence of severe skin reactions (e.g., SJS), probably as a consequence of CCR4$^+$ Treg depletion [146]. Other MoAbs targeting different regions and presumably different conformations of CCR4 have also been designed with the potential to specifically interfere with TARC/CCL17 or MDC/CCL22 activities [68]. The second approach consists in small-molecule CCR4 antagonists [61]. Despite encouraging data from pre-clinical models, none of these small molecules have been registered to date [145].

Studies investigating the functional and clinical impact of targeting the TARC/CCL17-CCR4 axis have been conducted in murine models and in humans for several of the aforementioned eosinophil-associated diseases (Table 4).

**Atopic dermatitis** In an ovalbumin-sensitized mouse model, the CCR4 antagonist compound 22 reduced AD-like lesions as well as CCR4$^+$ T cell infiltrates in the skin [147]. In a canine model of AD however, another antagonist (AZ445) was unable to significantly reduce skin lesions compared to CS, although CCR4$^+$ T cell numbers were locally reduced [148]. Similar antagonists are in development for humans [149]. Of note, the histamine H4 receptor antagonist (ZPL-3893787) which allegedly reduces TARC/CCL17 synthesis
| NCT number | Subjects/disease | Agent/drug class | Phase | Status | Results’ summary\(^a\) |
|------------|-----------------|------------------|-------|--------|------------------------|
| NCT01371812 HC | Non-malignant disorders | GSK2239633/small molecule | Phase I | Terminated | Low CCR4 blockade with the highest dose, not considered to be sufficiently effective for further development [200] |
| NCT01514981 AA | Non-malignant disorders | AMG 761/MoAb (mogamulizumab) | Phase I | Terminated | Prematurely terminated, frequent cutaneous side effects (not severe) (8 events in 18 subjects) |
| NCT04271514 AD and HC | Non-malignant disorders | RPT193/small molecule | Phase I | Recruiting | – |
| NCT00888927 Previously treated CTCL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase I/II | Terminated | No dose-limiting toxicity was observed. Among 38 evaluable patients, ORR was 36.8% [201] |
| NCT01728805 Relapsed or refractory CTCL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase III | Terminated | Higher PFS in KW-0761 vs vorinostat group (median 7.7 months [95% CI 5.7–10.3] vs 3.1 months [2.9–4.1] respectively) [154] |
| NCT00355472 Relapsed ATLL or PTCL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase I | Terminated | No dose-limiting toxicity was observed. |
| NCT01192984 Relapsed or refractory peripheral T/NK-cell Lymphoma | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase II | Terminated | ORR was 35% (95% CI 20% to 53%), median PFS was 3.0 months (95% CI, 1.6 to 4.9 months) [202] |
| NCT01611142 Relapsed or refractory PTCL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase II | Terminated | ORR was 11.4% (95% CI: 3.2–26.7%), disease control (SD or better) rate was 45.7% [203] |
| NCT00920790 Relapsed ATLL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase II | Terminated | ORR was 50% (95% CI, 30–70%), median PFS was 5.2 months and median OS 13.7 months [204] |
| NCT01626664 Relapsed or refractory ATLL | Malignant disorders | KW-0761/MoAb (mogamulizumab) | Phase II | Terminated | ORR was 14.9% in the KW-0761 group vs 0% with IC regimen [205] |
| NCT03602157 Relapsed or refractory CD30+ Hodgkin Lymphoma and Cutaneous T-Cell Lymphoma | Malignant disorders | CAR-T Cells Expressing CD30, CAR and CCR4 | Phase I | Recruiting | – |

\(^a\) If no citation indicated, data were collected from clinicaltrials.gov

AA allergic asthma, AD atopic dermatitis, ATLL adult T cell leukemia/lymphoma, CAR chimeric antigen receptor, CTCL cutaneous T cell lymphoma, HC healthy controls, IC investigator choice, MoAb monoclonal antibody, ORR overall response rate, PTCL peripheral T cell lymphoma, SD stable disease
producing T cells that drive the disease. cations as mogamulizumab could destroy the clonal IL-5-

by CS therapy. These results have potential therapeutic impli-

ations in mice, the only one tested in a phase I study in humans (GSK2239633) failed to induce sufficient CCR4 blockade at the highest dosing regimen [145]. Another phase I trial (NCT01514981) conducted with mogamulizumab was terminated prematurely due to drug-related adverse events. Finally, concerns have been raised regarding CCR4 blockade in asth-

ma, as Tregs also express this receptor and are reported to colonize lung tissue and to be functional in the effector phase (“recall”) of allergic inflammation in murine models and in humans following segmental allergen challenge [152, 153].

Allergic asthma To date, no therapy targeting TARC/CCL17 or CCR4 has been reported effective in human AA. In fact, among CCR4 antagonists shown to reduce allergic inflammation in mice, the only one tested in a phase I study in humans (GSK2239633) failed to induce sufficient CCR4 blockade at the highest dosing regimen [145]. Another phase I trial (NCT01514981) conducted with mogamulizumab was terminated prematurely due to drug-related adverse events. Finally, concerns have been raised regarding CCR4 blockade in asthma, as Tregs also express this receptor and are reported to colonize lung tissue and to be functional in the effector phase (“recall”) of allergic inflammation in murine models and in humans following segmental allergen challenge [152, 153].

T cell lymphoma Mogamulizumab was evaluated in a phase III randomized controlled trial in comparison with vorinostat in relapsed/refractory MF and SS. Patients in the mogamulizumab arm had significantly longer progression-free survival (PFS) compared to vorinostat (median PFS of 7.7 months versus 3.1 months respectively, HR 0.53 with 95% CI 0.41–0.59) [154]. Mogamulizumab has also shown efficacy in ATLL when combined with intensive chemother-

apy [155]. Indeed, its addition to background treatment resulted in improved PFS and overall survival, and it is now approved by Japanese authorities in newly diagnosed aggressive ATLL in combination with intensive chemotherapy [156].

L-HES Ledoult and colleagues recently reported that circulating CD3+CD4+ cells bear a Th2 chemokine receptor pheno-

type ex vivo defined as CCR4+CCR6+ in twenty patients with L-HES [157]. This phenotype was also expressed by 6 to 35% of CD3+CD4+ T cells from these patients and was not altered by CS therapy. These results have potential therapeutic implications as mogamulizumab could destroy the clonal IL-5-

producing T cells that drive the disease.

Conclusion and perspectives

Both pre-clinical data and the clinical observations described herein firmly establish the intimate link between the TARC/CCL17-CCR4 axis, type 2 immunity, and eosinophilic inflammation. As such, TARC/CCL17 represents a useful biomarker for diagnosis and assessment of disease activity for several allegedly T cell-driven eosinophilic disorders and may also help predict more severe disease forms and/or treat-

ment responses. Furthermore, overexpression/activation of this axis in these disorders makes it an appealing therapeutic target, as illustrated by the successful use of anti-CCR4 MoAb in certain T cell malignancies. Unfortunately, this approach has not yet produced results in the more common type 2 dis-

orders such as AD and AA, and the potential impact on CCR4-expressing Tregs is a subject of concern. Future studies focusing on the precise role played by TARC/CCL17 in various eosinophilic conditions, mechanisms involved in its over-

expression, CCR4 isoforms, and downstream signaling pathways will help determine whether the TARC/CCL17-CCR4 axis represents an interesting therapeutic target in non-

malignant disorders.

AA allergic asthma, CLA cutaneous lymphocyte antigen, DC dendritic cell

References

1. Genovese G, Di Zenzo G, Cozzani E, Berti E, Cugno M, Marzano AV (2019) New insights into the pathogenesis of bullous pemphi-

goid: 2019 Update. Front Immunol 10:1506

2. Yamada Y, Rothenberg ME, Lee AW, Akei HS, Brandt EB, Williams DA, Cancelas JA (2006) The FIP1L1-PDGFRα fusion 

gene cooperates with IL-5 to induce murine hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL)-like disease. Blood 107:4071–4079

3. Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP (2012) Molecular and clinical rationale for therapeutic targeting of 

interleukin-5 and its receptor. Clin Exp Allergy 42:712–737

4. Islam SA, Luster AD (2012) T cell homing to epithelial barriers in allergic disease. Nat Med 18:705–715

5. Imai T, Nagira M, Takagi S, Kakizaki M, Nishimura M, Wang J, Gray PW, Matsushima K, Yoshiie O (1999) Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. Int Immunol 11:81–88

6. Yoshiie O, Matsushima K (2015) CCR4 and its ligands: from bench to bedside. Int Immunol 27:11–20

7. Landheer J, de Bruin-Weller M, Boonacker C, Hijnen D, Bruijnzaal-Koomen C, Rickmann H (2014) Utility of serum thymus 

and activation-regulated chemokine as a biomarker for monitoring of atopic dermatitis severity. J Am Acad Dermatol 71: 

1160–1166

8. Ollila TA, Sahin I, Olszewski AJ (2019) Mogamulizumab: a new tool for management of cutaneous T-cell lymphoma. OncoTargets 

Ther 12:1085–1094
induces chemotaxis in eosinophils via its receptor CRTH2 and eosinophils may cause severe ocular inflammation in patients with allergic conjunctivitis. Cornea 24:S66–S70

31. Wong CK, Hu S, Cheung PFY, Lam CWK (2010) Thymic stromal lymphopoietin induces chemotactic and prosurvival effects in eosinophils: implications in allergic inammation. Am J Respir Cell Mol Biol 43:305–315

32. Liu LY, Jarjour NN, Busse WW, Kelly EAB (2003) Chemokine receptor expression on human eosinophils from peripheral blood and bronchoalveolar lavage fluid after segmental antigen challenge. J Allergy Clin Immunol 112:556–562

33. Yi S, Zhai J, Niu R et al (2018) Eosinophil recruitment is dynamically regulated by interleukin among lung dendritic cell subsets after allergen challenge. Nat Commun 9:3879

34. Nagase H, Kudo K, Izumi S, Ohta K, Kobayashi N, Yamaguchi M, Matsushima K, Morita Y, Yamamoto K, Hirai K (2001) Chemokine receptor expression profile of eosinophils at inflamed tissue sites: decreased CCR3 and increased CXCR4 expression by lung eosinophils. J Allergy Clin Immunol 108:563–569

35. Borchers MT, Ansay T, DeSalle R, Daugherty BL, Shen H, Metzger M, Lee NA, Lee JJ (2002) In vitro assessment of chemokine receptor-ligand interactions mediating mouse eosinophil migration. J Leukoc Biol 71:1033–1041

36. Bochner BS, Bickel CA, Taylor ML, MacGlashan DW, Gray PW, Raport CJ, Godiska R (1999) Macrophage-derived chemokine induces human eosinophil chemotaxis in a CC chemokine receptor 3- and CC chemokine receptor 4-independent manner. J Allergy Clin Immunol 103:527–532

37. Willkerson EM, Johansson MW, Hebert AS, Westphall MS, Mathur SK, Jarjour NN, Schwantes EA, Mosher DF, Coon JJ (2016) The peripheral blood eosinophil proteome. J Proteome Res 15:1524–1533

38. Larose M-C, Arambaut A-S, Provost V, Lavoie M, Flamand N (2017) Regulation of eosinophil and group 2 innate lymphoid cell trafficking in asthma. Front Med 4:136

39. Lee J, Rosenberg H (2013) Eosinophil secretory functions. In: Eosinophils Health Dis. Elsevier, pp 229–275

40. Ramírez GA, Yacoub M-R, Ripa M, Mannina D, Cariddi A, Savortini N, Ciceri F, Castagna A, Colombo G, Dagna L (2018) Eosinophils from physiology to disease: a comprehensive review. Biomed Res Int 2018:1–28

41. Curtis C, Ogbo P (2016) Hypereosinophilic syndrome. Clin Rev Allergy Immunol 50:240–251

42. Valent P, Kilon AD, Horny J-P et al (2012) Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol 130:607–612.e9

43. Chusid M, Dale D, West B, Wolff S (1975) The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) 54(1):1–27

44. Roufosse F, Weller PF (2010) Practical approach to the patient with hypereosinophilia. J Allergy Clin Immunol 126:39–44

45. Cools J, DeAngelo DJ, Gotlib J et al (2003) A tyrosine kinase inhibitor 3 is a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. J Biol Chem 278:45234–45241

46. Cogan E, Schadendorf D, Casaluxx P, Cochaux P, Velu T, Goldman M (1994) Brief report: clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. N Engl J Med 330: 535–538

47. Kilon AD (2015) How I treat hypereosinophilic syndromes. Blood 126:1069–1077

48. Inai T, Yoshida T, Baba M, Nishimura M, Kakizaki M, Yoshie O (1996) Molecular cloning of a novel T cell-directed CC chemokine expressed in thymus by signal sequence trap using Epstein-Barr virus vector. J Biol Chem 271:21514–21521
49. Imai T, Baba M, Nishimura M, Kakizaki M, Takagi S, Yoshie O (1997) The T cell-directed CC chemokine TARC is a highly specific biological ligand for CC chemokine receptor 4. J Biol Chem 272:15036–15042.

50. Nomiyama H, Imai T, Kusuda J, Miura R, Callen DF, Yoshie O (1997) Assignment of the human CC chemokine gene TARC (SCYA17) to chromosome 16q13. Genomics 40:211–213.

51. Alferink J, Lieberam I, Reindl W et al (2003) Compartmentalized production of CCL17 in vivo. J Exp Med 197:585–599.

52. Achuthan A, Cook AD, Lee M-C et al (2016) Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation. J Clin Invest 126:3453–3466.

53. Hsu AT, Lupancu TJ, Lee M-C, Fleetwood AJ, Cook AD, Hamilton JA, Achuthan A (2018) Epigenetic and transcriptional regulation of IL-4-induced CCL17 production in human monocytes and murine macrophages. J Biol Chem 293:11415–11423.

54. Medoff BD, Seung E, Hong S, Thomas SY, Sandall BP, Duffield JS, Kuperman DA, Erle DJ, Luster AD (2009) CD11b+ myeloid cells are the key mediators of Th2 cell homing into the airway in allergic inflammation. J Immunol 182:623–635.

55. Wimsberger G, Hebenstreit D, Posselt G, Horejs-Hoeck J, Duschl E. D (2000) Assignment of the human CC chemokine gene TARC/CCL17 to chromosome 16q13. Genomics 40:211–213.

56. Kakinuma T, Nakamura K, Wakugawa M, Yano S, Saeki H, Torii H, Komine T, Hieshima K, Nagakubo D, Sato E, Nakayama M, Koga T, Furue M, Yanagihara Y (2004) Reciprocal regulation of IL-4-induced expression of TARC/CCL17 and IP-10 (interferon-induced protein of 10kDa)/CXCL10 by TNF-α and IFN-γ in HaCaT cell line. Cytokine 20:1–6.

57. Sekiya T, Miymasusa M, Imanishi M et al (2000) Inducible expression of a Th2-type CC chemokine thymus- and activation-regulated chemokine by human bronchial epithelial cells. J Immunol Baltim Md 1950 165:2205–2213.

58. Berin MC, Eckmann L, Broide DH, Kagnoff MF (2001) Regulation of production of the T helper 2–Type T-cell chemotactic TARC by human bronchial epithelial cells in vitro and in human xenografts. Am J Respir Cell Mol Biol 24:382–389.

59. Nakayama T, Hieshima K, Nakagubo D, Sato E, Nakayama M, Kawa K, Yoshie O (2004) Selective induction of Th2-attracting chemokines CCL17 and CCL22 in human B cells by latent membrane protein 1 of Epstein-Barr virus. J Virol 78:1665–1674.

60. Fujii-Maeda S, Kajiwara K, Ikizawa K, Shinazawa M, Yu B, Koga T, Furue M, Yanagihara Y (2004) Reciprocal regulation of thymus and activation-regulated chemokine/macrophage-derived chemokine production by interleukin (IL)-4/IL-13 and interferon-γ in HaCaT keratinocytes is mediated by alterations in E-cadherin distribution. J Invest Dermatol 122:20–28.

61. Solari R, Pease JE (2015) Targeting chemokine receptors in disease – a case study of CCR4. Eur J Pharmacol 763:169–177.

62. Imai T, Chantry D, Raport CJ, Wood CL, Nishimura M, Godiska R, Yoshie O, Gray PW (1998) Macrophage-derived chemokine is a functional ligand for the cc chemokine receptor 4. J Biol Chem 273:1764–1768.

63. Vulcano M, Albanesi C, Stoppacciaro A et al (2001) Dendritic cells as a major source of macrophage-derived chemokine/ CCL22 in vitro and in vivo. Eur J Immunol 31:812–822.

64. Yamashita U, Kuroda E (2002) Regulation of macrophage-derived chemokine (MDC, CCL22) production. Crit Rev Immunol 22:105–114.

65. Hashimoto S, Nakamura K, Oyama N, Kaneko F, Tsunemi Y, Saeki H, Tamaki K (2006) Macrophage-derived chemokine (MDC)/CCL22 produced by monocyte derived dendritic cells reflects the disease activity in patients with atopic dermatitis. J Dermatol Sci 44:93–99.

66. D’Ambrosio D, Albanesi C, Lang R, Girolomoni G, Sinigaglia F, Laudanna C (2002) Quantitative differences in chemokine receptor engagement generate diversity in integrin-dependent lymphocyte adhesion. J Immunol 169:2303–2312.

67. Mariani M, Lang R, Bindl E, Panina-Bordignon P, D’Ambrosio D (2004) Dominance of CCL22 over CCL17 in induction of chemokine receptor CCR4 desensitization and internalization on human Th2 cells. Eur J Immunol 34:231–240.

68. Viney JM, Andrew DP, Phillips RM, Meiser A, Patel P, Lennartz-Walker M, Cousins DJ, Barton NP, Hall DA, Pease JE (2014) Distinct conformations of the chemokine receptor CCR4 with implications for its targeting in allergy. J Immunol 192:3419–3427.

69. Lin R, Choi Y, Zidar DA, Walker JK (2018) β-arrestin-2-dependent signaling promotes CCR4-mediated chemotaxis of murine T-helper type 2 cells. Am J Respir Cell Mol Biol 58:745–755.

70. Weston CA, Rana BMJ, Cousins DJ (2019) Differential expression of functional chemokine receptors on human blood and lung group 2 innate lymphoid cells. J Allergy Clin Immunol 143:410–413.e9.

71. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD (2018) Atopic dermatitis. Nat Rev Dis Primer 4:1.

72. Oldhoff JM, Darsow U, Werfel T et al (2005) Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 60:693–696.

73. Kang EG, Narayana PK, Pouliquen IJ, Lopez MC, Ferreira-Cornwell MC, Geczy JA (2020) Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis. Allergy 75:950–953.

74. Saeki H, Tamaki K (2006) Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. J Dermatol Sci 43:75–84.

75. Kakinuma T, Nakamura K, Wakugawa M et al (2001) Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. J Allergy Clin Immunol 107:535–541.

76. Rubin LA, Nelson DL (1990) The soluble interleukin-2 receptor: biology, function, and clinical application. Ann Intern Med 113:619–627.

77. Vestergaard C, Bang K, Gesser B, Yoneyama H, Matsushima K, Larsen CG (2000) A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA+CCR4+ lymphocytes into lesional atopic dermatitis skin. J Invest Dermatol 115:640–646.

78. Wakugawa M, Nakamura K, Kakinuma T, Onai N, Matsushima K, Tamaki K (2001) CC chemokine receptor 4 expression on peripheral blood CD4+ T cells reflects disease activity of atopic dermatitis. J Invest Dermatol 117:188–196.

79. Jang M, Kim H, Kim Y, Choi J, Jeon J, Hwang Y, Kang JS, Lee WJ (2016) The crucial role of IL-22 and its receptor in thymus and activation regulated chemokine production and T-cell migration by house dust mite extract. Exp Dermatol 25:598–603.

80. Zhang Y-Y, Wang A-X, Xu L, Shen N, Zhu J, Tu C-X (2016) Characteristics of peripheral blood CD4+CD25+ regulatory T cells and related cytokines in severe atopic dermatitis. Eur J Dermatol 26:240–246.

81. Husain Z, Reddy BY, Schwartz RA (2013) DRESS syndrome. J Am Acad Dermatol 68:693.e1–693.e14.

82. Ogawa K, Morito H, Hasegawa A et al (2013) Identification of thymus and activation-regulated chemokine (TARC/CCL17) as a potential marker for early indication of disease and prediction of disease activity in drug-induced hypersensitivity syndrome (DHS)/drug rash with eosinophilia and systemic symptoms (DRESS). J Dermatol Sci 69:38–43.

83. Ogawa K, Morito H, Hasegawa A et al (2014) Elevated serum thymus and activation-regulated chemokine (TARC/CCL17) relates to reactivation of human herpesvirus 6 in drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). Br J Dermatol 171:425–427.
84. Watanabe H (2018) Recent advances in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. J Immunol Res 2018:1–10
85. Lin L, Hwang B-J, Culoen DA et al (2018) Eosinophils mediate tissue injury in the autoimmune skin disease bullous pemphigoid. J Invest Dermatol 138:1032–1043
86. Kakinuma T, Wakugawa M, Nakamura K, Hino H, Matsushima K, Tamaki K (2003) High level of thymus and activation-regulated chemokine in blister fluid and sera of patients with bullous pemphigoid. Br J Dermatol 148:203–210
87. Miyashiro D, Sanches JA (2020) Erythroderma: a prospective study of 309 patients followed for 12 years in a tertiary center. Sci Rep 10:9774
88. Nakano-Tahara M, Terao M, Nishioka M, Kitaba S, Murota H, Katayama I (2015) T Helper 2 polarization in senile erythroderma with elevated levels of TARC and IgE. Dermatology 230:62–69
89. Ohga Y, Bayaraa B, Imafuku S (2018) Chronic idiopathic hypersensitivity pneumonia: a review of the literature. Jpn J Clin Immunol 130:1404–1412.e7
90. Murayama T, Nakamura K, Tsuchida T (2015) Eosinophilic pustulosis of the scalp in adults. J Am Acad Dermatol 72:e13–e17
91. Zhang L, Qi R, Yang Y, Gao X, Chen H, Xiao T (2019) Serum levels of Th2 cytokines and Th1 cytokines in patients with eosinophilic granulomatosis with polyangiitis. Int J Immunopathol Pharmacol 32:12
92. Tapia B, Morel E, Martin-Diaz M-A, Diaz R, Alves-Ferreira J, Rubio P, Padial A, Bellon T (2007) Up-regulation of CCL17, CCL22 and CCR4 in drug-induced maculopapular exanthema. Clin Exp Allergy J Br Soc Allergy Clin Immunol 37:704–713
93. Quaglino P, Caproni M, Antiga E et al (2007) Serum levels of the IL-12/23 and IL-17 pathway cytokines in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 119:1553–1559.e4
94. Teraki Y, Taguchi R (2014) Serum TARC levels correlate with soluble Fas ligand expression in patients with chronic urticaria. J Dermatol Sci 74:90–93
95. Terakawa T, Sato H, Yoneyama Y et al (2005) Serum levels of Th1 cytokines and Th2 cytokines in patients with H1N1 influenza A virus infection. Jpn J Infect Dis 58:9–13
96. Chen R, Smith SG, Salter B, El-Gammal A, Oliveria JP, Obminski E, Buser R, Conquet F, Proudfoot AEI, Wells TNC, Power CA (2000) A key role for CC chemokine receptor 4 in lipopolysaccharide-induced endotoxic shock. J Exp Med 191:1755–1763
97. Kawasaki S, Takizawa H, Yoneyama H et al (2001) Intervention of Th2 cytokines and eosinophilic granulomatosis with polyangiitis attenuates the development of allergic airway inflammation and hyperresponsiveness in mice. J Immunol 166:2055–2062
98. Hart D, Latzin P, Buser R, Conquet F, Proudfoot AEI, Wells TNC, Power CA (2000) A key role for CC chemokine receptor 4 in lipopolysaccharide-induced endotoxic shock. J Exp Med 191:1755–1763
99. Bochner BS, Hudson SA, Xiao HQ, Liu MC (2003) Release of eosinophil-derived neurotoxin in patients with relapsing eosinophilic granulomatosis with polyangiitis. Allergy 58:1085–1091
100. Perros F, Hoogsteden HC, Coyle AJ, Lambrecht BN, Hammad H (2009) Blockade of CCR4 in a humanized model of asthma reveals a critical role for DC-derived CCL17 and CCL22 in attracting Th2 cells and inducing airway inflammation. Allergy 64:995–1002
101. Heijink IH, Marcel Kies P, van Oosterhout AJM, Postma DS, Kauffman HF, Vellenga E (2007) Der p, IL-4, and TGF-β cooperatively induce EGFR-dependent TARC expression in airway epithelium. Am J Respir Cell Mol Biol 36:351–359
102. Miyazaki E, Nureki S, Fukami T, Shigenaga T, Ando M, Ito K, Ando H, Sugisaki K, Kumamoto T, Tsuda T (2002) Elevated
levels of thymus- and activation-regulated chemokine in bronchoalveolar lavage fluid from patients with eosinophilic pneumonia. Am J Respir Crit Care Med 165:1125–1131

120. Miyazaki E, Nureki S, Ono E, Ando M, Matsuno O, Fukami T, Ueno T, Kumamoto T (2007) Circulating thymus- and activation-regulated chemokine/CCL17 is a useful biomarker for discriminating acute eosinophilic pneumonia from other causes of acute lung injury. Chest 131:1726–1734

121. Nureki S, Miyazaki E, Ando M, Kumamoto T, Tsuda T (2005) CC chemokine receptor 4 ligand production by bronchoalveolar lavage fluid cells in cigarette-smoke-associated acute eosinophilic pneumonia. Clin Immunol 116:83–93

122. Katoh S, Fukushima K, Matsumoto N, Matsumoto K, Abe K, Onai N, Matsushima K, Matsukura S (2003) Accumulation of CCR4-expressing CD4+ T cells and high concentration of its ligands (TARC and MDC) in bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. Allergy 58:518–523

123. Nakagome K, Shoda H, Shirai T, Nishihara F, Soma T, Uchida Y, Sakamoto Y, Nagata M (2017) Eosinophil transendothelial migration induced by the bronchoalveolar lavage fluid of acute eosinophilic pneumonia: eosinophil accumulation in AEP. Respirology 22:913–921

124. Hristov AC, Tejasvi T, Wilcox RA (2019) Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management. Am J Hematol 94:1027–1041

125. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C, Tamaki K, Kakinuma T, Saeki H et al (2006) Serum levels of Kakinuma T, Sugaya M, Nakamura K, Kaneko F, Wakugawa M, Sugaya M, Morimura S, Suga H, Kawaguchi M, Miyagaki T, Lefèvre G, Copin M-C, Staumont-Sallé D et al (2014) The lymphoid variant of the hypereosinophilic syndrome. J Allergy Clin Immunol 124:1319–1325.e3

126. Suzuki M, Yamauchi Y, Nakamura K, Kanaoka M, Matsukura S, Takahashi K, Takahashi Y, Kambara T, Aihara M (2020) Serum thymus and activation-regulated chemokine (TARC/CCL17) may be useful to predict the disease activity in patients with bullous pemphigoid. J Eur Acad Dermatol Venereol. https://doi.org/10.1111/jdv.16851

127. Machida H, Inoue S, Shibata Y et al (2021) Thymus and activation-regulated chemokine (TARC/CCL17) predicts decline of pulmonary function in patients with chronic obstructive pulmonary disease. Allergol Int 70:81–88

128. Latzin P, Hartl D, Regamey N, Frey U, Schoeni MH, Casaula C (2008) Comparison of serum markers for allergic bronchopulmonary aspergillosis in cystic fibrosis. Eur Respir J 31:36–42

129. Shono Y, Suga H, Kamijo H, Fujii H, Oka T, Miyagaki T, Shishido-Takahashi N, Sugaya M, Sato S (2019) Expression of CCR3 and CCR4 suggests a poor prognosis in mycosis Fungoides and Sézary syndrome. Acta Derm Venereol 99:809–812

130. Ishida T, Utsumoiyama A, Iida S, Inagaki H, Utsunomiya A, Komatsu H, Iida S, Takeuchi G, Eimoto T, Nakamura S, Ueda R (2004) CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinico-pathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res 10:5494–5500

131. Thilen C, Radermacher V, Trimeche M, Roufosse F, Goldman M, Boniver J, de Leval L (2008) TARC and IL-5 expression correlates with tissue eosinophilia in peripheral T-cell lymphomas. Leuk Res 32:1431–1438

132. Yoshie O, Fujisawa R, Nakayama T et al (2002) Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood 99:1505–1511

133. Roufosse F, Cogan E, Goldman M (2007) Lymphoctic variant hypereosinophilic syndrome. Immunol Allergy Clin N Am 27:389–413

134. Lefèvre G, Copin M-C, Staumont-Sallé D et al (2014) The lymphoid variant of hypereosinophilic syndrome: study of 21 patients with CD3–CD4+ aberrant T-cell phenotype. Medicine (Baltimore) 93:255–266

135. Carpentier C, Verbanck S, Schandène L, Heimann P, Trépant A-L, Cogan E, Roufosse F (2020) Eosinophilia associated with CD3–CD4+ T cells: characterization and outcome of a single-center cohort of 26 patients. Front Immunol 11:1765

136. de Lavareille A, Roufosse F, Schandène L, Stordeur P, Cogan E, Goldman M (2001) Clonal Th2 cells associated with chronic hypereosinophilia: TARC-induced CCR4 down-regulation in vivo. Eur J Immunol 31:1037–1046

137. de Lavareille A, Roufosse F, Schandène L, Cogan E, Simon H-U, Goldman M (2002) High serum thymus and activation-regulated chemokine levels in the lymphoctic variant of the hypereosinophilic syndrome. J Allergy Clin Immunol 110:476–479

138. Ogbogu PU, Bechner BS, Butterfield JH et al (2009) Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol 124:1319–1325.e3

139. Suzuki M, Yamauchi Y, Nakamura K, Kanaoka M, Matsukura S, Takahashi K, Takahashi Y, Kambara T, Aihara M (2020) Serum thymus and activation-regulated chemokine (TARC/CCL17) may be useful to predict the disease activity in patients with bullous pemphigoid. J Eur Acad Dermatol Venereol. https://doi.org/10.1111/jdv.16851
152. Faustino L, da Fonseca DM, Takenaka MC, Mirotti L, Florsheim EB, Guereschi MG, Silva JS, Basso AS, Russo M (2013) Regulatory T cells migrate to airways via CCR4 and attenuate the severity of airway allergic inflammation. J Immunol Baltim Md 190:2614–2621

153. Afshar R, Strassner JP, Seung E, Causton B, Cho JL, Harris RS, Hamilos DL, Medoff BD, Luster AD (2013) Compartamentalized chemokine-dependent regulatory T-cell inhibition of allergic pulmonary inflammation. J Allergy Clin Immunol 131:1644–1652

154. Kim YH, Bagot M, Pinter-Brown L et al (2018) Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 19:1192–1204

155. Ishida T, Jo T, Takemoto S et al (2015) Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukemia-lymphoma: a randomized phase II study. Br J Haematol 169:672–682

156. Cook LB, Fuji S, Hermine O et al (2019) Revised Adult T-Cell Leukemia-Lymphoma International Consensus Meeting Report. J Clin Oncol 37:677–687

157. Ledoult E, Groh M, Kahn J-E et al (2020) Assessment of T-cell polarization on the basis of surface marker expression: diagnosis and potential therapeutic implications in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol Pract 8:1110–1114.e2

158. Liddiard K, Welch JS, Lozach J, Heinz S, Glass CK, Greaves DR (2006) Interleukin-4 induction of the CC chemokine TARC (CCL17) in murine macrophages is mediated by multiple STAT6 sites in the TARC gene promoter. BMC Mol Biol 7:45

159. Fujimura T, Kambayashi Y, Furudate S, Asano M, Kakizaki A, Nakanishi T, Inaba M, Inagaki-Katashiba N, Tanaka A, Vien Watanabe S, Homma T, Yamaguchi M, Takeuchi H, Adachi M, Kurokawa M, Matsukura S, Kawaguchi M, Ieki K, Suzuki S, Osabe M, Tajika T, Tokhin M (2018) Allopurinol suppresses expression of the regulatory T-cell migration factors TARC/CCL17 and MDC/CCL22 in HaCaT keratinocytes via restriction of nuclear factor-κB activation. J Appl Toxicol JAT 38:274–283

159. Ledoult E, Groh M, Kahn J-E et al (2020) Assessment of T-cell polarization on the basis of surface marker expression: diagnosis and potential therapeutic implications in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol Pract 8:1110–1114.e2

160. Soumelis V, Reichenbach E, Kanzler H et al (2002) Human epithelial cells trigger dendritic cell-mediated allergic inflammation by producing TSLP. Nat Immunol 3:29–36

161. Nakanishi T, Inaba M, Inagaki-Katashiba N, Tanaka A, Vien Watanabe S, Homma T, Yamaguchi M, Takeuchi H, Adachi M, Kurokawa M, Matsukura S, Kawaguchi M, Ieki K, Suzuki S, Osabe M, Tajika T, Tokhin M (2018) Allopurinol suppresses expression of the regulatory T-cell migration factors TARC/CCL17 and MDC/CCL22 in HaCaT keratinocytes via restriction of nuclear factor-κB activation. J Appl Toxicol JAT 38:274–283

162. Zhou B, Comeau MR, Smedt TD, Liggitt HD, Dahl ME, Lewis EB, Guereschi MG, Silva JS, Basso AS, Russo M (2013) IL-4-expressing bronchoalveolar T cells from asthmatic and healthy subjects preferentially express CCR3 and Th2 cytokines to induce optimal levels of TARC/CCL17. J Immunol 189:1648–1658

163. Terada N, Nomura T, Kim WJ et al (2001) Expression of C-C chemokine TARC in human nasal mucosa and its regulation by cytokines. Clin Histol Glymphast Asciamp Exp Allergy 31:1923–1931

164. Biedermann T, Schirwitzl C, Lametschwandtner G, Thoma G, Carballido-Perrig N, Kud J, de Vries JE, Rot A, Carballido JM
Inaoki M, Sato S, Shirasaki F, Mukaida N, Takehara K (2003) The frequency of type 2 CD8+ T cells is increased in peripheral blood from patients with psoriasis vulgaris. J Clin Immunol 23:269–278

Ahern D, Lloyd CM, Robinson DS (2009) Chemokine responsiveness of CD8+ CD25+ regulatory and CD8+ CD25- T cells from atopic and nonatopic donors. Allergy 64:1121–1129

Lim HW, Lee J, Hillsamer P, Kim CH (2008) Human Th17 cells share major trafficking receptors with both polarized effector T cells and FOXP3+ regulatory T cells. J Immunol 180:122–129

Trifari S, Kaplan CD, Tran EH, Crelin NK, Spits H (2009) Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from TH-17, TH1 and TH2 cells. Nat Immunol 10:864–871

Mjösberg JM, Trifari S, Crelin NK, Peters CP, van Drunen CM, Piet B, Fokkens WJ, Cupedo T, Spits H (2011) Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol 12:1055–1062

Salimi M, Barlow JL, Saunders SP et al (2013) A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. J Exp Med 210:2939–2950

Amin K, Janson C, Harvima I, Venge P, Nilsson G (2005) CC chemokine receptors CCR1 and CCR4 are expressed on airway mast cells in allergic asthma. J Allergy Clin Immunol 116:1383–1388

Bratke K, Priesench C, Garbe K, Kuepper M, Lommatsch M, Virchow JC (2013) Plasmacytoid dendritic cells in allergic asthma and the role of inhaled corticosteroid treatment. Clin Exp Allergy 43:312–316

Vittorakis S, Samitas K, Tousa S, Zervas E, Aggelakopoulou M, Semitekolou M, Panoutsakopoulou V, Xanthou G, Gaga M (2014) Circulating conventional and plasmacytoid dendritic cell subsets display distinct kinetics during in vivo repeated allergen skin challenges in atopic subjects. Biomed Res Int 2014:231036

Bonner K, Pease JE, Corrigan CJ, Clark P, Kay AB (2013) CCL17/thymus and activation-regulated chemokine induces cationic gene-related peptide in human airway epithelial cells through CCR4. J Allergy Clin Immunol 132:942–950.e1–3

Harl D, Lee CG, Da Silva CA, Chupp GL, Elias JA (2009) Novel biomarkers in asthma: chemokines and chitinase-like proteins. Curr Opin Allergy Clin Immunol 9:60–66

Sekiya T, Yamada H, Yamaguchi M, Yamamoto K, Iishi A, Yoshie O, Sano Y, Morita A, Matsushima K, Hirai K (2002) Increased levels of a TH2-type CC chemokine thymus and activation-regulated chemokine (TARC) in serum and induced sputum of asthmatics. Allergy 57:173–177

Leung TF, Wong CK, Lam CWK, Li AM, Ip WK, Wong GWK, Fok TF (2003) Plasma TARC concentration may be a useful marker for asthmatic exacerbation in children. Eur Respir J 21:616–620

Abou El-Ela M, El-Rifae AE-A, Fawzi M, Abdel Hay R, Gohary Y, Shaker O (2011) Thymus and activation-regulated chemokine in different stages of mycosis fungoides: tissue and serum levels: TARC in mycosis fungoides. Australas J Dermatol 52:167–171

Inagaki A, Ishida T, Yano H et al (2008) Clinical significance of serum TARC/CCL17 in ATLL patients: high TARC/CCL17 level is a significant unfavorable prognostic factor. Blood 112:2821–2821

Cahn A, Hodgson S, Wilson R et al (2013) Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK2239633, a CC-chemokine receptor 4 antagonist, in healthy male subjects: results from an open-label and from a randomised study. BMC Pharmacol Toxicol 14:14

Duvic M, Pinter-Brown LC, Foss FM et al (2015) Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood 125:1883–1889

Ogura M, Ishida T, Hatake K et al (2014) Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-CC chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol 32:1157–1164

Zinzani PL, Karlin L, Radford J et al (2016) European phase II study of mogamulizumab, an anti-CCR4 monoclonal antibody, in relapsed/refractory peripheral T-cell lymphoma. Haematologica 101:e407–e410

Ishida T, Joff T, Uike N et al (2012) Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol Off J Am Soc Clin Oncol 30:837–842

Phillips AA, Fields P, Hermine O et al (2016) A prospective, multicenter, randomized study of anti-CCR4 monoclonal antibody mogamulizumab (moga) vs investigator’s choice (IC) in the treatment of patients (pts) with relapsed/refractory (R/R) adult T-cell leukemia-lymphoma (ATL). J Clin Oncol 34:7501–7501

McCormick SM, Gowda N, Fang JX, Heller NM (2016) PI3Kδ is a significant unfavorable prognostic factor. Blood 112:2821–2821

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.