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REVIEW

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

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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 cytoplasmic 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

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HHV	Human herpes virus
ICOG-Eo	International Cooperative Working Group on Eosinophil Disorders
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
ILC2	Type 2 innate lymphoid cell
LC	Langerhans cell
LN	Lymph node
MDC	Macrophage-derived chemokine
MF	Mycosis fungoides
MoAb	Monoclonal antibody
NFkB	Nuclear factor-kappa B
PBMC	Peripheral blood mononuclear cell
PDGFRA	Platelet-derived growth factor receptor A
PFS	Progression free survival
PGD2	Prostaglandin D2
PTCL	Peripheral T cell lymphoma
PI3K	Phosphatidylinositol 3-kinase
SCORAD	Scoring atopic dermatitis
SJS	Stevens-Johnson syndrome
SS	Sézary syndrome
STAT	Signal transducer and activator of transcription
TARC	Thymus and activation-regulated chemokine
TGF	Transforming growth factor
TK	Tyrosine kinase
TNF	Tumor necrosis factor
Treg	Regulatory T cell
TSLP	Thymic stromal lymphopoietin
VCAM	Vascular cell adhesion molecule

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 Sezary 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 naïve 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

accomplish their effector functions. This recruitment to inflamed tissue involves selective expression of integrins, selectins, and chemokine receptors depending on their state of activation and differentiation [4]. For example, circulating $CCR8^+$ CD4 T cells from healthy humans produce more IL-5 (a characteristic of highly differentiated Th2 cells) than $CCR4^+$ CD4 T cells in which IL-4 is predominant [14]. Other chemoattractant factors for human and murine Th2 cells include IL-33, CCL17, CCL18, CCL20, CCL22, CXCL10, CX3CL1, leukotriene B4, and prostaglandin D2 (PGD2) [4, 15].

The effector functions of Th2 cells in tissue are largely mediated by the canonical type 2 cytokines IL-4, IL-5, and IL-13 which orchestrate the early and late phases of allergic disease. Interleukin-4 favors isotype class-switching within allergen-specific B cells, leading to production of IgE-type immunoglobulins. By binding to the FcεRI expressed on mast cells and basophils, allergen-specific IgE induces degranulation and release of an array of mediators that account for the typical manifestations of allergic reactions [9]. Interleukin-13 induces goblet cell hyperplasia, mucus secretion, smooth muscle contraction, and subepithelial fibrosis [16].

Interleukin-5 is critically involved in the constitution of eosinophilic inflammation. In healthy humans, eosinophils account for 3–5% of blood leucocytes and are easily recognizable by their bilobed nucleus and their cytoplasmic eosinavid granules. They originate in the bone marrow (BM), where common myeloid progenitors give rise to eosinophilic progenitors (hEoP) characterized by surface expression of the IL-5 receptor alpha chain (IL-5Rα, CD125) that will be preserved throughout their life-cycle [17]. Human EoP will become mature eosinophils through mechanisms relying on the expression of several transcription factors (GATA-1, C/EBPα, C/EBPε, and PU-1) and growth factors including IL-5, IL-3, and granulocyte macrophage colony stimulating factor (GM-CSF) [18, 19].

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 0.5×10^9/L, while the term hypereosinophilia (HE) applies when an AEC above 1.5×10^9/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].

Hypereosinophilia 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 (PDGFRA) fusion gene, which encodes a constitutively active tyrosine kinase (TK) [45]. Reactive (HES_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-α) 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-α and interferon (IFN)-γ that act synergistically in a nuclear factor-kappa B (NFκB)-dependent manner [56–58], consistent with the presence of a NFκB 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

Table 1 Sources and mechanisms of TARC/CCL17 synthesis

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/JAK3, STAT6, JMJD3, 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	[103[a], 159]
Myeloid DCs	Human, $CD11c^+$ DCs	TSLP, TSLP + RANK or CD40 engagement	/	/	[160, 161]
	Mouse, $CD11c^+$ DCs	TSLP	/	/	[162]
		IL-33	/	ERK1/2, JNK, p38 MAPK,	[163]
		IL-4, IL-13	/	STAT6	[54]
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	/	STAT6, NFκB, MEK, JNK	[32]
$CD3^+$ T cells	Human, HC	IL-4	/	STAT6	[55]
$CD4^+CD45RA^+$ T cells	Human, AA patients	PBMC stimulation with Der f allergen OR with anti-CD3 + CD28 Abs	Anti-CD80 + CD86 Abs	/	[104]
Keratinocytes	Human	TNF-α + IFN-γ[b]	IL-4, IL-13, TGF-β, Casuarinin, Spinasterol Glc, Allopurinol, Roxithromycin	p38 MAPK, Raf1, JAK2, STAT1, NFκB	[56, 60, 166–171]
		HDM extract, IL-22	/	STAT3, ERK, AKT	[79]
	Human, Mouse	GITR engagement	/	NFκB	[172]
Bronchial epithelial cells	Human	TNF-α + IFN-γ +/- IL-1α[b]	Glucocorticoids, Long-acting β-2 adrenergic agonist	NFκB	[57, 58, 173]
		TNF-α + IL-4 + IFN-γ[b]			
		IL-4 alone: weak or no effect			
		Der p alone	/	ADAM-dependent EGFR phosphorylation, p38 MAPK, ERK1/2, NFκB	[101]
		IL-4 + TGF-β			
		Der p + IL-4 + TGF-β (highest response)			
		IL-4 alone: no effect			
		TLR3 ligand poly(I:C)[c]	/	/	[174]
		TWEAK + TGF-β1 during EMT	/	/	[175]
Alveolar epithelial cells	Human	TNF-α or IL-1α alone	Glucocorticoids	NFκB, STAT6	[57, 58, 176]
		TNF-α or IL-1α or IFN-γ + IL-4 or IL-13[b]			
		RSV + IL-4 or IL-13[b]			
		IL-4/IL-13 alone: no effect			
Nasal epithelial cells	Human, allergic volunteers and HC	TNF-α + IL-4 or IL-13	/	/	[177]
Airway smooth muscle cells	Human	IL-4 or IL-13 + TNF-α	β-adrenergic agonist (isoproterenol), no effect of glucocorticoids	/	[178]
		IL-4/IL-13 alone: no effect			
Dermal endothelial cells	Human	IL-4 or IL-13 + TNF-αIL-4/IL-13 alone: no effect	No effect of glucocorticoids	p38 MAPK, NFκB	[179]
Dermal fibroblasts	Human	IL-4 or IL-13 + TNF-α (enhanced by IFN-γ)	No effect of glucocorticoids	/	[166, 179]
		IL-4/IL-13 alone: no effect			

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* epitheliomesenchymal 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, *JMJD* Jumonji C domain-containing proteins, *JNK* Janus kinase, *LC* Langerhans cell, *LPS* lipopolysaccharide, *MAPK* mitogen-activated protein kinases, *MEK* mitogen-activated protein/extracellular signal-regulated kinase kinase, *NFKB* nuclear factor-kappa B, *PGN* peptidoglycans, *PI3K* 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

[a] In this study, macrophages demonstrated a partial M2 phenotype

[b] A synergistic effect appears when cells are co-stimulated with these agents

[c] A synthetic analog of viral dsRNA

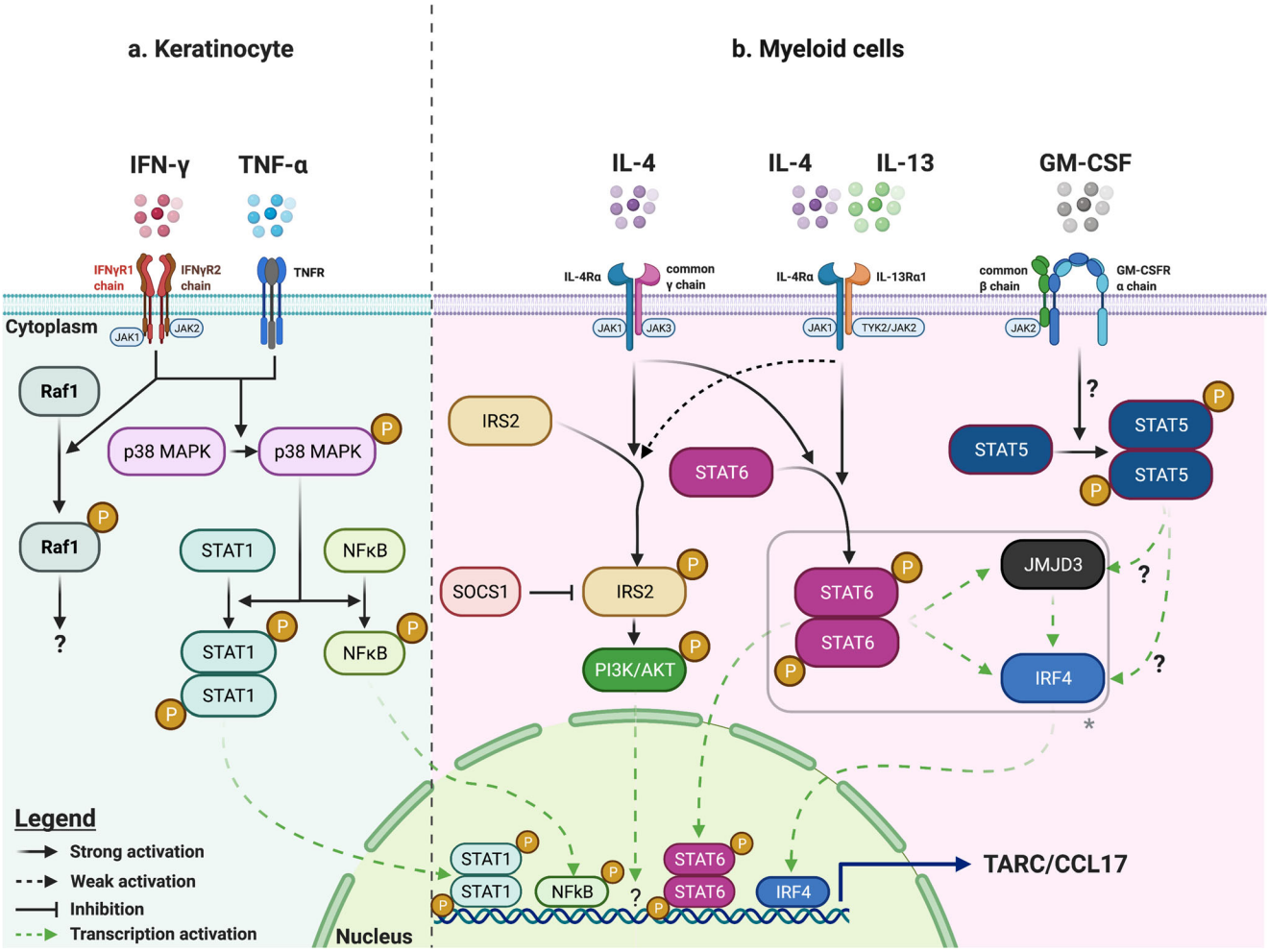

Fig. 1 Identified molecular mechanisms underlying TARC/CCL17 synthesis in selected cell types. Mechanisms involved in induction of TARC/CCL17 synthesis are shown schematically for **a** human keratinocyte cell lines (HaCaT) and **b** human monocytes and murine bone marrow–derived macrophages. In HaCaT cells, TNF-α and IFN-γ induce JAK2, p38 MAPK, and Raf-1 activation by phosphorylation after ligation to their dedicated receptors [168, 170]. Subsequently, activated p38 MAPK phosphorylates STAT1 and NFκB, inducing their activation and translocation into the nucleus to trigger TARC/CCL17 synthesis [169]. **b** In human monocytes and murine macrophages, IL-4 and IL-13-induced phosphorylation and homodimerization of STAT6 (following engagement of both types of IL-4 receptors) triggers TARC/CCL17 expression directly by binding the *TARC* gene promoter [53, 206]. In addition, activated STAT6 increases transcription of IRF4 and JMJD3, and the latter induces the demethylation of repressive H3K27me3 in the *IRF4* promoter region, resulting in enhanced expression of the transcription factor IRF4 that binds directly to the TARC/CCL17 promoter (*the latter mechanism is demonstrated after IL-4 but not IL-13-induction of STAT6) [53]. A similar pathway is involved in GM-CSF-induced TARC/CCL17 transcription, probably through STAT5 activation [52]. Engagement of the type 1 IL-4Rα/common-γ chain heterodimeric receptor by IL-4 also recruits IRS2, inducing its phosphorylation and activation. In turn, IRS2 phosphorylates/activates the PI3K/AKT pathway, ultimately leading to TARC/CCL17 transcription [206]. SOCS1 expression is also induced by IL-4 in healthy human monocytes and has been shown to interact directly with IRS2 and downregulate its activity, through ubiquitination and proteasomal degradation [206]. This figure was created with BioRender.com. IFN interferon, IL interleukin, IRF interferon regulatory factor, IRS insulin receptor substrate, JAK Janus kinase, JMJD3 Jumonji domain-containing protein D3, MAPK mitogen-activated protein kinases, NFκB nuclear factor-kappa B, PI3K phosphatidylinositol 3-kinase, STAT signal transducer and activator of transcription, SOCS suppressor of cytokine signaling protein, TNF tumor necrosis factor, TYK tyrosine kinase

[68]. 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 synthetize 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 dermoepidermal 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-22Rα at their surface. Activation of the IL-22/IL-22Rα 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 (Tc2)	[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 (ILC2s)	[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[a] of sTARC/CCL17 increase	Principal cellular source of TARC/CCL17	Correlation(s) of sTARC with other biomarkers/clinical features[b]	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 (+) Serum sCD25	Assessment and monitoring of disease severity Prediction (in most cases) of severe disease course at diagnosis	[7, 56, 74, 165]
DRESS	Skin Serum Mean 31,259 pg/ml (SEM ±6374)	CD11c+ DCs	(+) Blood eosinophils (+) Serum sCD25 (+) Skin lesions severity	Differentiation with other drug-induced skin reactions (SJS, maculopapular erythema) Association btw 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 (+) Urticaria/erythema scores	Disease activity monitoring (earlier elevation than anti-BP180 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[c] (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 465–673)	Not assessed	(+) A. *fumigatus*-specific IgE (+) Recombinant A. *fumigatus* allergen f4-IgE (–) FEV_1	Differentiation btw ABPA and aspergillus sensitization or colonization in CF Earlier detection of disease onset compared with total IgE kinetics	[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 No correlation with AEC	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)	[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	Site/magnitude[a] of sTARC/CCL17 increase	Principal cellular source of TARC/CCL17	Correlation(s) of sTARC with other biomarkers/clinical features[b]	Potential clinical implications	Refs
	Median10,855 pg/mL (range 3466–422,787)			sTARC > 3000 pg/ml: 100% sensitivity and 75% specificity ($p<0.0001$) for $CD3^-CD4^+$ L-HES among patients with F/P^- HES Predictive of OCS-responsiveness, and suboptimal biological response to mepolizumab	

AA allergic asthma, *ABPA* allergic broncho-pulmonary aspergillosis, *AD* atopic dermatitis, *AEC* absolute eosinophil count, *AEP* acute eosinophilic pneumonia, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *BALF* bronchoalveolar lavage fluid, *btw* between, *CCL26* CC chemokine 6, *CCR4* CC chemokine receptor 4, *CF* cystic fibrosis, *DC* dendritic cell, *DRESS* drug reaction eosinophilia and systemic symptoms, *EGPA* eosinophilic granulomatosis with polyangiitis, *FeNO* fractional exhaled nitric oxide, FEV_1 forced expiratory volume in one second, *F/P* Fip 1-like 1 (*FIP1L1*)/platelet-derived growth factor receptor alpha (*PDGFRA*) fusion gene, *HES* hypereosinophilic syndrome, *HHV-6* human herpes virus 6, *IgE ILC2s*, type 2 innate lymphoid cells, immunoglobulin E, *IQR* interquartile range, *LDH* lactate dehydrogenase, *L-HES* lymphoid variant HES, *MDC* macrophage-derived chemokine, *MF* mycosis fungoides, *OCS* oral corticosteroid therapy, *OS* overall survival, *PEFR* peak expiratory flow rate, *PFS* progression free survival, Refs references, *SEM* standard error of the mean, *SJS* Steven-Johnson syndrome, *SS* Sezary syndrome, *(s)TARC* (serum)thymus and activation-regulated chemokine, *Th2* cells type 2 helper T cells, *sCD25* serum soluble IL-2Ralpha

[a] sTARC in healthy controls: median 243 pg/ml (range 34-973from 143); mean: 220,6 pg/mL (± SEM 27.9 pg/ml)[115]

[b] (+): positive correlation, (−) negative correlation

[c] Type 2-high status was defined as the mucosal expression of CCL26 gene, periostin gene and a multigene IL-13 *in vitro* signature

Senile erythroderma Erythroderma is a debilitating skin disease defined as more than 90% of skin surface affected by erythema and scaling. More than a quarter of patients with erythroderma have peripheral eosinophilia [87]. Erythroderma may be idiopathic or secondary, occurring in the setting of disorders such as psoriasis, atopy, drug hypersensitivity (including DRESS), MF, or SS, most of which are associated with elevated sTARC/CCL17. In one series of 68 patients with erythroderma aged 65 years or older, of which 53% had a detectable secondary cause, sTARC/CCL17, serum IgE, and the level of blood and tissue eosinophilia did not differ between idiopathic and secondary subgroups [88]. Interestingly, patients with senile erythroderma (predominantly male in this study) had lower IgE levels and a lower ratio of antigen-specific IgE/total IgE but higher levels of sTARC/CCL17 than patients with AD suggesting that IgE synthesis in this disorder is the consequence of a Th2 shift independent of specific allergens [88, 89].

Other skin disorders Elevated sTARC/CCL17 levels have been reported sporadically in several other dermatological disorders, namely, eosinophilic pustular folliculitis [90], chronic spontaneous urticaria [91], maculopapular exanthema [92], and Stevens-Johnson syndrome/toxic epidermal necrolysis (although levels are significantly lower than in DRESS) [93]. Patients with non-episodic angioedema with eosinophilia were shown to have elevated sTARC/CCL17 levels at presentation that regressed in parallel with AEC in response to corticosteroid (CS) therapy in one study [94]. In episodic angioedema, serum TARC levels are also elevated and cycle with disease activity as discussed below [95].

Pulmonary disorders

Allergic asthma (AA) is a chronic respiratory disease often characterized by eosinophilic inflammation of the airways together with increased mucus secretion and bronchial hyperreactivity. The underlying type 2 immune response combines ILC2s that represent an early source of type 2 cytokines after allergen challenge and Th2 cells [96]. Consistent with the key role of eosinophils in a subgroup of patients, biologics targeting IL-5 and its receptor reduce exacerbations and improve lung function in severe eosinophilic asthma and have been approved as add-on therapies in this indication [97].

The TARC/CCL17-CCR4 axis has been well studied in asthma, since it contributes at least partially to Th2 cell recruitment to the lung. Ex vivo allergen challenge of human bronchial explants has been shown to induce synthesis of functionally active TARC/CCL17 in patients with asthma but not HC [98]. Furthermore, several studies in asthmatic patients have reported induction of TARC/CCL17 in bronchoalveolar lavage fluid (BALF) after allergen challenge [99, 100]. Cellular sources of TARC/CCL17 in this context include not only bronchial and alveolar epithelial cells [57, 58, 101] but also $CD11c^+$ DCs

[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 polyangiitis (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 within 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 $CD3^-CD4^+TCR\alpha/\beta^-$) and produce type 2 cytokines including IL-5 [132], explaining its classification as HES_R. Common clinical manifestations include skin lesions, angioedema, lymphadenopathy, and rheumatological involvement [133, 134]. In a study investigating chemokine receptor expression on these naturally occurring human Th2 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-PDGFRA-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

Table 4 Clinical trials evaluating anti-CCR4 agents in healthy subjects, non-malignant and malignant disorders

NCT number	Subjects/disease	Agent/drug class	Phase	Status	Results' summary[a]
Non-malignant disorders					
NCT01371812	HC	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	AMG 761/MoAb (mogamulizumab)	Phase I	Terminated	Prematurely terminated, frequent cutaneous side effects (not severe) (8 events in 18 subjects)
NCT04271514	AD and HC	RPT193/small molecule	Phase I	Recruiting	–
Malignant disorders					
NCT00888927	Previously treated CTCL	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	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	KW-0761/MoAb (mogamulizumab)	Phase I	Terminated	No dose-limiting toxicity was observed.
NCT01192984	Relapsed or refractory peripheral T/NK-cell Lymphoma	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	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	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	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	CAR-T Cells Expressing CD30, CAR and CCR4	Phase I	Recruiting	–

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

[a] If no citation indicated, data were collected from clinicaltrials.gov

[150] was tested in subjects with AD in a randomized, double-blind, placebo-controlled trial and was shown to reduce the SCORAD score and eczema area and severity index (EASI), but not pruritus [151].

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 chemotherapy [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 phenotype 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 treatment 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 disorders 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 overexpression, 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

Code availability Not applicable.

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Declarations

Competing interests FR has received consultancy fees from GlaxoSmithKline and AstraZeneca, and royalties from UpToDate.

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