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REVIEW ARTICLE

CLA$^+$ memory T cells in atopic dermatitis

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Abstract

Circulating skin-homing cutaneous lymphocyte-associated antigen (CLA)$^+$ T cells constitute a small subset of human memory T cells involved in several aspects of atopic dermatitis: *Staphylococcus aureus* related mechanisms, the abnormal Th2 immune response, biomarkers, clinical aspects of the patients, pruritus, and the mechanism of action of targeted therapies. Superantigens, IL-13, IL-31, pruritus, CCL17 and early effects on dupilumab-treated patients have in common that they are associated with the CLA$^+$ T cell mechanisms in atopic dermatitis patients. The function of CLA$^+$ T cells corresponds with the role of T cells belonging to the skin-associated lymphoid tissue and could be a reason why they reflect different mechanisms of atopic dermatitis and many other T cell mediated skin diseases. The goal of this review is to gather all this translational information of atopic dermatitis pathology.

KEYWORDS
atopic dermatitis, biomarker, CLA$^+$ T cells, skin-homing, translational

Abbreviations: AD, atopic dermatitis; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; CLA, cutaneous lymphocyte-associated antigen; CRTH2, chemokine receptor Th2; CTACK, T cell-attracting chemokine; EASI, eczema area and severity index; GM-CSF, granulocyte macrophage colony-stimulating factor; HDM, house dust mite; HLA, human leucocyte antigen; ICAM-1, intercellular adhesion molecule-1; ICOS, inducible T cell costimulatory; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cells; LDH, lactate dehydrogenase; LFA-1, lymphocyte function-associated antigen-1; Mab, monoclonal antibody; MDC, macrophage-derived chemokine; PSGL-1, P-selectin glycoprotein ligand-1; *S. aureus*, *Staphylococcus aureus*; Sag, superantigen; SALT, skin-associated lymphoid tissue; SEB, staphylococcal enterotoxin B; TARC, thymus and activation-regulated chemokine; Tc, cytotoxic T cell; T_{cm}, central memory T cell; TCR, T-cell receptor; T_{em}, effector memory T cell; Th, helper T cell; TNF, tumor necrosis factor; T_{reg}, regulatory T cell; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4.

1 | CLA EXPRESSION ON HUMAN T CELLS AND SKIN

The cutaneous lymphocyte-associated antigen (CLA) is a cell surface molecule preferentially expressed on human memory T cells infiltrating skin (over 90% of skin infiltrating T cells), in inflamed and non-inflamed situations, that it is not expressed on T cells infiltrating extra-cutaneous sites.[1] CLA is a carbohydrate, a modified form of sialyl Lewis X antigen,[2] and is an epitope of the surface protein P-selectin glycoprotein ligand-1 (PSGL-1).[3] It can be found on different human T-cell populations such as CD45RO$^+$ memory CD4$^+$ and CD8$^+$ T cells, effector/central T cells[4] and it is expressed on about 15% of peripheral blood T cells of healthy individuals.[1] In human CDR45RO$^+$ T cells CLA is upregulated during the naïve to memory transition by fucosyltransferase VII.[5] Other T-cell subsets such as Vγ9Vδ2 T cells[6] and NKG2D$^+$ CD8$^+$ T cells[7] express CLA. In addition, CLA is also expressed by regulatory T cells (T_{reg}),[8] Type 2 innate lymphoid cells (ILC)2[9] and ILC3,[10] and effector memory B cells.[11] Nevertheless, at present, the functional implications in atopic dermatitis (AD) of other T-cell types expressing CLA, besides the CD45RO$^+$ subset, have not been clarified. CLA has been shown to be induced by the effect of interleukin (IL)-12 on freshly generated helper T cells (Th)1/cytotoxic T cells (Tc)1 and Th2/Tc2 cells,[12] ex vivo in human Th2 cells,[13] as well as, by staphylococcal enterotoxin B (SEB).[14]

1.1 | CLA$^+$ T cells in skin migration and skin-blood recirculation

Most T cells that home to skin are of the CD45RO$^+$ phenotype and express CLA.[1] CLA functions as an adhesion molecule when is recognized by the lectin domain of the E-selectin present on endothelial cells.[2,15] Additional molecular interactions are required to mediate transendothelial migration of CLA$^+$ T cells through the superficial vascular plexus.[16,17] Adhesion interactions (lymphocyte function-associated antigen-1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1), and very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1)) together with chemokines binding to their receptors are necessary (Figure 1). The keratinocyte-derived C-C chemokine ligand (CCL)27/CTACK (T cell-attracting chemokine) binds to C-C motif chemokine receptor (CCR)10, that is preferentially expressed on CLA$^+$ T cells.[18,19] Similarly, CCL17/TARC (thymus and activation-regulated chemokine), one of the best biomarkers of AD,[20] binds to CCR4, which is preferentially expressed by CD4$^+$ CLA$^+$ memory T cells.[21]

Efalizumab, a LFA-1 targeting monoclonal antibody (Mab) that blocks the LFA-1/ICAM-1 interaction, was formerly a candidate medication for AD that led to clinical improvement[22] and reduction of cutaneous CLA$^+$ memory T cells.[23] During treatment, patients developed a secondary CLA$^+$ lymphocytosis that, after treatment discontinuation, led to disease exacerbation. Such phenomenon demonstrated normal T cell recirculation/turnover between peripheral tissues (e.g., skin) and blood. In that context, inflammatory tissue "resident" memory T cells can migrate back from the skin to the blood[24] and display a CLA$^+$ Th2 signature with increased expression of GATA3 and IL-13.[25] Thus, the relevance of circulating CLA$^+$ T cells in dermatology not only relies on their capacity to selectively migrate to skin, but also on their de-homing ability (Figure 1), implying that these circulating memory T cells might reflect cutaneous immune responses.[26] Consistently, it has been shown that CLA$^+$ memory/effector T cells can be found in draining lymphatics of the skin.[27–29] This feature, added to the positive correlation between the phenotype and amount of circulating CLA$^+$ T cells and AD severity, and the abundant infiltrates of CLA$^+$ T cells in AD lesional skin (compared to controls),[30] suggests that circulating CLA$^+$ T cells may serve as cellular peripheral biomarkers in AD.[31]

CLA$^+$ T cells also represent activated immune cells that can migrate to various tissues and induce an inflammatory response. Similar types of cellular migration have been demonstrated in the circulation of patients with various chronic inflammatory diseases.[32–34] Allergen-specific T cells have been reported at a frequency of one in 10^4–10^5 T cells; however, a Type 2 immune response in allergies and asthma is not solely confined to allergen-specific T cells. It harbors a wider skew in immune response including skin-homing CLA$^+$ Type 2 T cells, chemokine receptor Th2 (CRTH2)-expressing type T cells, ILC2, B cells and CRTH2$^+$ eosinophils.[32,35,36] The migration of activated T cells to other target organs of inflammation has been demonstrated in food allergen-specific and skin-homing T cells that are sensitized in the gut and can migrate into the skin causing AD.[34] Circulating T cells are highly active in polyallergic patients and express chemokine receptors for the migration to many different tissues.[37] Such a mechanism could be responsible for the atopic march of allergic diseases in the sequential order of AD, food allergy, asthma, and allergic rhinitis.[38,39]

These findings are in line with the epithelial barrier theory that proposes that environmental exposure to certain substances, such as detergents, surfactants, toothpastes, food emulsifiers and additives, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles and microplastics, might be toxic to our cells.[40–42] CLA$^+$ T cells have been proposed to be activated in the gut and migrate to skin. Disturbed gut barriers by environmental substances may lead to local T cells activation, which gain a skin-homing capacity and migrate to AD skin. The barrier theory describes that pathogen colonization, particularly *Staphylococcus aureus* (*S. aureus*), altered microbiota diversity, local inflammation, and incorrect regeneration and remodelling, take place in tissues with a compromised epithelial barrier. A myriad of chronic inflammatory diseases develop and worsen as a consequence of inflammatory cells migration to remote tissues, which also contributes to tissue damage and inflammation in distant organs.[43]

1.2 | CLA$^+$ T cells in the human cutaneous immune response

The skin-associated lymphoid tissue (SALT) was proposed by J. W. Streilein 40 years ago based on several pieces of evidence, among

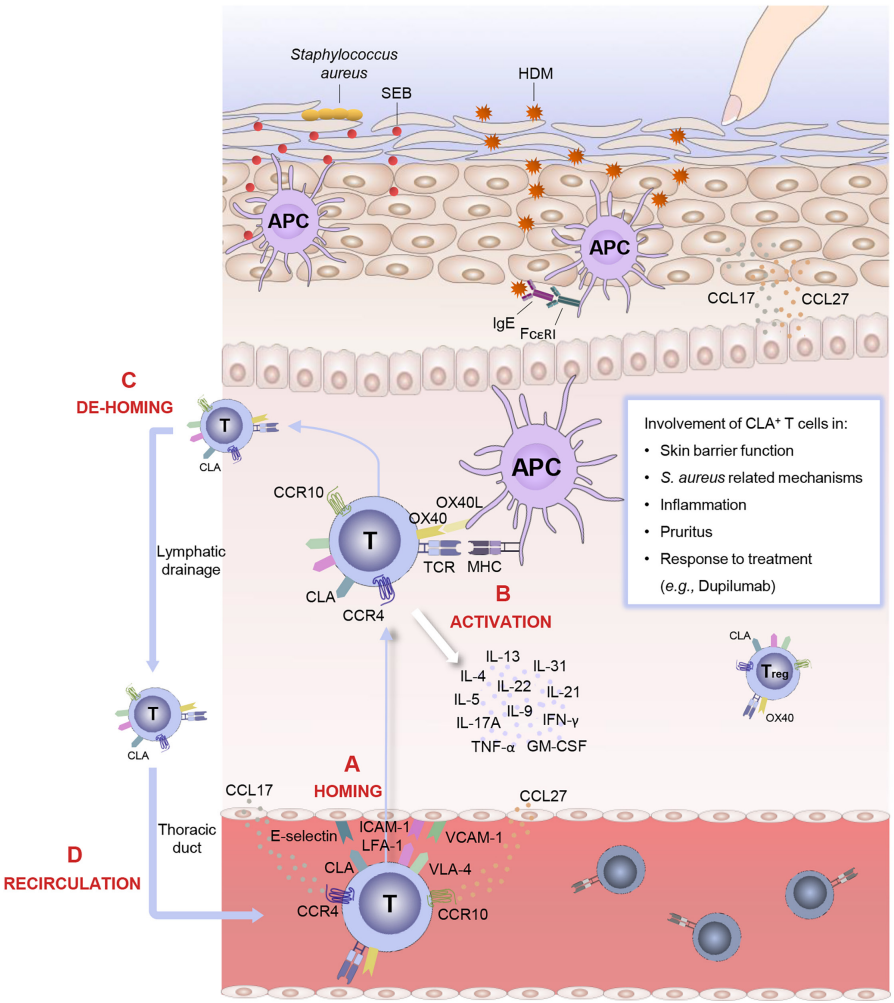

FIGURE 1 Circulating CLA$^+$ memory T cells in the pathological mechanisms of AD. Skin-homing CLA$^+$ T cells migrate into the skin (A) through a multistep process based on molecular interactions of CLA, LFA-1 and VLA-4 expressed on T cells, with E-selectin, ICAM-1 and VCAM-1 respectively, present on cutaneous endothelial cells. Additional interactions between CCR4 and CCR10 expressed on CLA$^+$ T cells, and their ligands CCL17 and CCL27 respectively, produced by keratinocytes, are required during this process. Local activation of CLA$^+$ T cells (B) implies their involvement in the cutaneous immune response and, by virtue of their de-homing (C) and skin-blood recirculation capacities (D), they reflect in the periphery the cutaneous abnormalities present in AD lesions, including *S. aureus* related mechanisms, abnormal Th2 immune response dominated by IL-13, and pruritogenic IL-31. Interestingly, an early effect of dupilumab in AD treated patients is only reflected on circulating CLA$^+$, but not CLA$^-$, CD4$^+$ CCR4$^+$ T cells. APC, antigen presenting cell; CLA, cutaneous lymphocyte-associated antigen; HDM, house dust mite; MHC, major histocompatibility complex; *S. aureus*, *Staphylococcus aureus*; SEB, staphylococcal enterotoxin B; TCR, T-cell receptor.

TABLE 1 Similarities of skin-associated lymphoid tissues (SALT) and CLA$^+$ T cells properties.

SALT[44] properties	CLA$^+$ T cells properties
Only a subset of T cells displays skin affinity.	Selective skin homing.
Skin-related lymphocytes produce immunoregulatory molecules.	Memory phenotype with broad capacity for cytokine production.
Immune recognition of antigen in the skin.	Preferentially respond to antigens related to skin.

Abbreviations: CLA, cutaneous lymphocyte-associated antigen; SALT, skin-associated lymphoid tissues.

others, the existence of T cells with skin affinity and the ability to recognize skin-associated antigens.[44] Based on the skin tropism, recirculation, and specific responses of CLA$^+$ T cells, it may be considered that this population constitutes the subset of CD45RO$^+$ population that is closer to SALT features and may be contemplated representative of the skin-associated adaptive immune system (Table 1).[26]

Since the discovery of the CLA antigen numerous human studies have confirmed the implication of circulating CLA$^+$, but not CLA$^-$, memory T cells in diverse T cell-mediated cutaneous diseases with various pathological mechanisms. In this sense, circulating CLA$^+$ T cells respond to antigens, allergens, viruses, bacterial superantigens and drugs, and their phenotype has been reported to correlate with the clinical activity and response to treatment of cutaneous diseases (Table 2).[26] For instance, in cutaneous T-cell lymphoma, CLA is expressed on tumorigenic CCR4$^+$ CD4$^+$ T cells[48]; in dengue, CLA is upregulated in virus-specific effector CD4$^+$ and CD8$^+$ T cell populations the day before defervescence[59]; in herpes simplex, CLA is selectively expressed on circulating virus-specific CD8$^+$ T cells, which are involved in viral clearance in the skin[51]; in papuloerythroderma, circulating CD4$^+$ and CD8$^+$ T cells preferentially express the CLA marker and produce IL-4, IL-13, IL-22 and IL-31, that decrease after clinical remission[55]; and in plaque psoriasis, the response to *Streptococcus pyogenes* is confined to CLA$^+$ T cells with an IL-17 response that correlates with the clinical status of the patients.[56]

2 | CLA$^+$ T CELLS IN AD

AD is characterized by a compromised skin barrier, abnormal cutaneous immune responses, altered microbiota, and intense pruritus. Translational knowledge derived from the efficacy and mechanism of targeted therapies in AD patients has allowed identifying key disease pathways, such as Th2-derived cytokines IL-13, IL-4 and IL-31 and IL-22.[61–63] The majority of infiltrating cells in AD lesional skin are CD3$^+$ CD4$^+$ CD45RO$^+$ CLA$^+$ T cells,[30,64] which are related to different aspects of AD, including clinical features, response to treatment, and biomarkers (Figure 1).

2.1 | CLA$^+$ T cells in the clinical context of the AD patient

Circulating CD4$^+$ and CD8$^+$ CLA$^+$ T cells from AD patients express increased levels of CD25, CD40 ligand, human leucocyte antigen (HLA)-DR and inducible T cell costimulator (ICOS),[31,32,65] and spontaneously proliferate due to their in vivo activation phenotype. Additionally, long term T-cell HLA-DR activation in skin-homing cells is increased in adults with AD compared to psoriasis patients or controls.[65] Circulating CD4$^+$ and CD8$^+$ CLA$^+$ T cells also express the major Type 2 cytokines IL-4, IL-5, and IL-13,[66] as well as, IL-9, IL-17A, IL-21 IL-22, IL-31, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and granulocyte macrophage colony-stimulating factor (GM-CSF).[4,67–69]

CLA$^+$ T cells contribute to Th2 immune response by induction of immunoglobulin (Ig)E production by B cells and enhance eosinophil survival.[32,65,70] Production of IFN-γ by skin-homing T cells is one of the main mechanisms of eczema formation due to keratinocyte apoptosis. IFN-γ is mainly induced by IL-12, an important mediator for the direction of the immune response towards IFN-γ production. IL-12 is produced by keratinocytes and dendritic cells in the microenvironment.[71,72]

Patients with AD show increased frequencies of CLA expression and selective CLA$^+$ Th2/Tc2 and Th22/Tc22 expansion,

TABLE 2 Relationship between CLA$^+$ T cell biology and skin diseases besides atopic dermatitis.

Human skin diseases	Involvement of CLA$^+$ T cells
Acute graft versus-host disease	Upregulated expression of CLA on CD38^{bright} CD8$^+$ T cells.[45]
Allergic contact dermatitis	Response to nickel, cobalt, and chromium metal allergy.[46]
Alopecia areata	Th2/Tc2 activation.[47]
Cutaneous T-cell lymphoma	CLA expression on tumorigenic CCR4$^+$ CD4$^+$ T lymphocytes.[48]
Drug-induced allergic reactions	Response to drugs.[49]
Guttate psoriasis	*Streptococcus pyogenes* induces Th17 response.[50]
Herpes Simplex	CD8$^+$ T anti-viral response.[51]
Leprosy	Antigen-specific response.[52]
Lichen planus	CLA$^+$ T cells are present in lesions of oral lichen planus and oral lichenoid reactions.[53]
Melanoma	Skin metastasis and response to therapy.[54]
Papuloerythroderma	Higher proportion than CLA$^-$ of IL-4, IL-13, IL-22 and IL-31 production.[55]
Plaque Psoriasis	Response to *Streptococcus pyogenes* and relation with clinical status.[56]
Rosacea	Response to demodex[57]
Scleroderma	CD8$^+$ CLA$^+$ T cells producing IL-13 accumulate in lesions and produce cytotoxic granules.[58]
Skin dengue infection	Response to Dengue.[59]
Vitiligo	Response to autoantigens.[60]

Abbreviation: CLA, cutaneous lymphocyte-associated antigen.

accompanied by selective CLA$^+$ Th1/Tc1 reduction in blood.[68] Focusing on memory subsets, applying CLA positivity classification, AD immune activation involves not only of CLA$^+$ T cells but also of CLA$^-$ or 'systemic' T-cell subset. Compared to psoriasis, another inflammatory skin disease,[73] 'systemic'/CLA$^-$ and more prominently CLA$^+$ CD45RO$^+$CCR7$^+$ central memory (T_{cm}) and CLA$^+$ CD45RO$^+$CCR7$^-$ effector memory (T_{em}) T cells were significantly more activated in AD patients.[65] Additionally, frequencies of IL-13-producing CLA$^+$ T cells and circulating CLA$^+$ T_{em} and T_{cm} cells significantly correlated with disease severity and total IgE levels in serum of AD patients, exemplifying how CLA$^+$ frequencies may reflect several disease aspects. One such blood phenotyping study comparing adults and children with AD showed that in young children of less than 5 years old there is a dominant signature of CLA$^+$ Th2 cells, with CLA$^+$ Th1 reductions, while other immune changes build up with time and disease chronicity.[67] These results point to the Th2 dominance in early AD and support the importance of addressing this immune axis when treating young populations.

Exacerbations of AD are occasionally associated with exogenous environmental triggers.[74] The defective skin barrier prompts allergen/antigen penetration leading to specific responses of cutaneous T lymphocytes. The response to allergens such as house dust mite (HDM) is restricted to CLA$^+$ T cells in AD.[73] Intriguingly, a recent study has shown that the T-cell receptor (TCR) repertoire of circulating allergen-specific CLA$^+$, but no CLA$^-$, T cells highly overlaps with that found in T cells infiltrating AD lesions,[75] raising evidence for circulating CLA$^+$ T cells as relevant T cells infiltrating the skin that respond to allergens locally.

Epigenetic modifications have been suggested as possible contributors to AD pathogenesis.[76] Acevedo et al. showed that in AD patients, CD4$^+$ CLA$^+$ memory T cells are characterized by dysregulated epigenetic signatures affecting key cytokine signaling pathways, with a reduced DNA methylation in the upstream region of *IL13* gene that correlates with increased *IL13* mRNA expression in these cells. Based on this, the epigenetic alteration in the *IL13* promoter may account for the augmented ability of CD4$^+$ CLA$^+$ T cells to produce IL-13 in AD.[30] Altogether these data suggest that CLA$^+$ T cells play a central role in the initiation and perpetuation of AD.[77]

2.2 | *S. aureus* and CLA$^+$ T cell interaction in AD

Staphylococcus aureus colonizes approximately 90% AD lesional and non-lesional skin compared to only 10% of healthy subjects[78] and is linked to AD flare up.[79] *Staphylococcus aureus* is involved in microbial dysbiosis, skin barrier abnormalities and T cell-mediated inflammation.[79] Importantly, *S. aureus*-colonized AD patients have a distinct phenotype and endotype with more severe disease.[80] SEB superantigen (Sag) is the most prevalent in AD[81] and it is associated with disease severity.[82] Application of SEB to intact AD skin induces dermatitis.[83] There is a strong mechanistic association between Sags and CLA$^+$ T cells, since *S. aureus*-reactive TCR Vβ skewing is found preferentially in circulating CD4$^+$ and CD8$^+$ CLA$^+$ T cells from AD patients and not controls,[84,85] and an increased percentage of CLA$^+$ T cells bearing TCR Vβ for *S. aureus* Sags is found in children with AD.[86]

Sags, compared to conventional antigens, induce T-cell expression of CLA via an IL-12 dependent mechanism[14] and contribute to AD skin inflammation by activating large numbers of T cells in lesional skin. This process is important in increasing the population of memory T cells that are capable of efficient extravasation to skin and maintaining continuous T-cell activation in the skin and thus perpetuate AD lesions even when the initiating allergen cannot be demonstrated or absent from the current environment. In a coculture model between circulating memory T cells and autologous epidermal cells from AD lesions, SEB induced preferential activation of CLA$^+$, rather than CLA$^-$, T cells leading to broad production of T-cell-derived mediators present in AD lesions (IL-13, IL-4, IL-17A, and IL-22), with IL-13 the highest Th2 cytokine produced.[87] This goes in line with the dominant IL-13 pathways,[88] as well as the increased IL-13 protein expression over IL4,[89] found in AD lesional skin. Furthermore, the same study reported that IL-13 was the only mediator that positively correlated with patients' eczema area and severity index (EASI), plasma levels of CCL17 and IgE against *S. aureus*, and CCL26 mRNA expression in cutaneous lesions (Figure 2).[87] Overall, these data are supported by the fact that IL-13 is the key Th2 cytokine with a wide impact on disease pathogenesis.[90] α-toxin, which is also produced by *S. aureus*, has also been reported to induce an enhanced IL-22 secretion by peripheral blood mononuclear cells and CD4$^+$ T cells from AD patients compared to patients with psoriasis and controls.[91]

2.3 | CLA$^+$ T cell relationship with AD biomarkers and targeted therapies

While AD diagnosis is still mostly based on clinical criteria, there is an ongoing search for reproducible, minimally invasive, reliable, and valid biomarkers.[20,92] Over 100 different markers have been suggested as biomarkers in AD. The most reliable biomarker reported is serum CCL17.[20]

The CLA$^+$ T cells and CCL17 functions are related mechanisms in AD (Figure 2), since CCR4, the receptor for CCL17, is preferentially expressed on circulating CLA$^+$ CD4$^+$ memory T cells[21] and T_{reg}.[93] In support of this, CLA$^+$ memory Th2 cells from AD patients selectively migrate to human skin grafts transplanted onto severe combined immunodeficient mice in response to CCR4.[94] Two independent pediatric studies have shown that increased levels of skin CCL17 may predict AD development in infancy.[95,96] The preferential Th2 response by CLA$^+$ T cells,[4] along with the link between skin CCL17 and disease development and the positive correlation between serum CCL17 and disease severity,[97] is in line with the pathological role of CLA$^+$ T cells in pediatric AD population. In addition, in adults a recent phase 1b study has shown that the oral CCR4-antagonist RPT193 led to clinical improvement in moderate-to-severe AD.[98] On its behalf, CCL27, that is a CLA$^+$ T

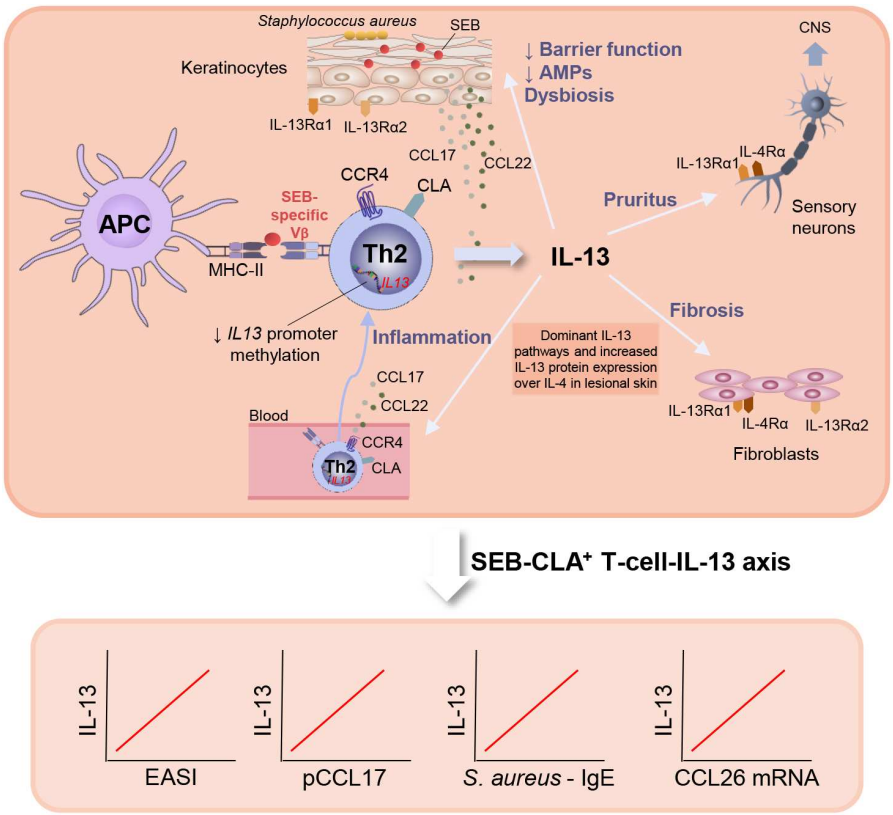

FIGURE 2 IL-13, SEB and CCL17 mechanisms meet in CLA$^+$ T cell biology in AD. SEB-specific TCR Vβ are preferentially expressed by CLA$^+$ T cells that upon activation induce a predominant IL-13 response in the skin where abundant expression of IL-13Rα1 and IL-13Rα2 is found. Lesional skin presents dominant IL-13 pathways, with increased IL-13 expression over IL-4, that are involved in skin barrier dysfunction, dysbiosis, pruritus, inflammation, and fibrosis. CLA$^+$ CD4$^+$ T cells in AD present an epigenetic alteration for IL-13, and the SEB-CLA$^+$ T-cell-IL-13 axis relates to patients' severity and plasma levels of IgE to *S. aureus*. Only IL-13, but not other SEB-induced cytokines, correlates with plasma levels of CCL17, one of the best biomarkers for AD, which is a ligand for CCR4 that attracts circulating CLA$^+$ CD4$^+$ CCR4$^+$ Th2 cells to skin. Additionally, IL-13 correlates with CCL26 mRNA expression in lesional skin. AMPs, antimicrobial peptides; APC, antigen presenting cell; CLA, cutaneous lymphocyte-associated antigen; CNS, central nervous system; EASI, eczema area and severity index; MHC-II, major histocompatibility complex class II; *S. aureus*, *Staphylococcus aureus*; SEB, staphylococcal enterotoxin B.

cells attracting chemokine, has been shown to be increased in the stratum corneum and associated with disease severity in pediatric AD.[99]

One potential issue for biomarkers in AD is that they differ among diverse populations. Circulating CLA$^+$ T cells have been shown to correlate with AD immune skewing across ages and ethnicities, and thus their applicability is not limited by disease chronicity and/or patient demographics. Other suggested biomarkers include E-selectin, CCL22/MDC (macrophage-derived chemokine), lactate dehydrogenase (LDH), IL-18, IL-13, among others.[20] Serum IgE, commonly measured in AD patients, was suggested as a disease biomarker, however it is only moderately correlated with AD severity, and while CLA is applicable in both intrinsic (normal IgE levels) and extrinsic (high IgE levels) AD patients, IgE measures and correlations with disease severity are mainly relevant in extrinsic AD patients,[100] a fact that limits its use as a biomarker.

Another consideration is the accessibility to the biomarker (blood, skin, tape stripping etc.), along with the requisite for repeated sampling. Biomarkers obtained from tape stripping or skin biopsies, as well as biomarkers that correlate with AD comorbidities, were investigated.[101] The fact that CLA$^+$ T cells are effortlessly extracted from peripheral blood tests puts them under the category of minimally invasive biomarkers.[20] Moreover, their ability to predict and monitor therapeutic responses reinforces their potential as cellular peripheral biomarkers in AD.[31] The fully human monoclonal IgG4 antibody dupilumab was shown to improve clinical, molecular and barrier measures in moderate-to-severe AD patients. Bakker et al. showed a significant reduction in the proliferation (Ki67 positivity) and decrease in production of IL-4, IL-5, IL-13, and IL-22 before and during treatment with dupilumab, limited to circulating CD4$^+$ CLA$^+$ T cells, supporting CLA$^+$ T-cell responses as a surrogate measure to dupilumab efficacy.[102,103] Besides this, recent multiparametric flow cytometry studies identified increased IL-13$^+$ CLA$^+$ cells in AD patients treated with dupilumab during clinical remission when compared to healthy controls.[104]

The OX40-OX40L axis has recently attracted attention in AD due to the improvements shown for both anti-OX40 depleting antibodies telazorlimab (GBR 830)[105] and rocatinlimab (KHK4083),[106] added to the non-depleting monoclonal antibody amlitelimab (KY1005) that binds to OX40L present on antigen presenting cells.[107] The

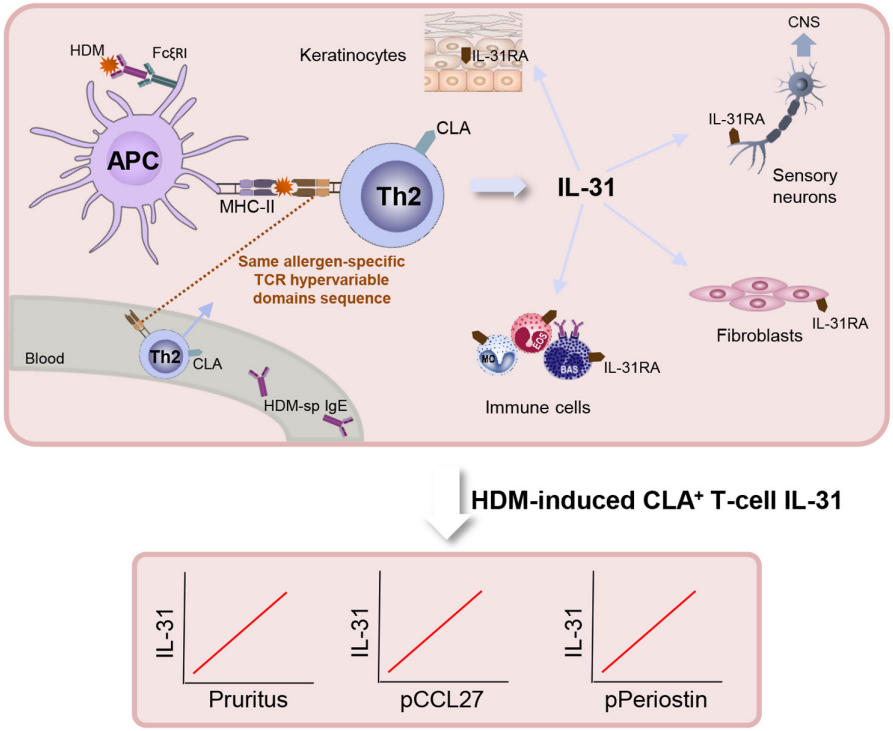

FIGURE 3 HDM specifically induces CLA$^+$ T cell IL-31, which correlates with patient's pruritus. Circulating CLA$^+$ T cells preferentially respond to HDM and share with infiltrating HDM-specific T cells same TCRB CDR3 regions. CD4$^+$ CLA$^+$ T cells are the most abundant lymphocytic population in AD lesions and major producers of IL-31. HDM-induced IL-31 by circulating CLA$^+$ T cells correlates with patient's pruritus intensity, and plasma levels of periostin, in patients with HDM-specific IgE. Additionally, plasma levels of the keratinocyte-derived chemokine CCL27, a ligand for CCR10 that is preferentially expressed by CLA$^+$ T cells, correlate with HDM-induced CLA$^+$ T cell IL-31 response. Interestingly, CCL27 in the stratum corneum is a biomarker of response to anti-IL31RA therapy in AD. APC, antigen presenting cell; CLA, cutaneous lymphocyte-associated antigen; CNS, central nervous system; HDM, house dust mite; HDM-sp IgE, IgE specific for house dust mite; MHC-II, major histocompatibility complex class II.

OX40-OX40L interaction is involved in long-term and optimal cell activation of CD4$^+$ T cells and favors expansion and survival of Th2 cells.[105] OX40 is highly expressed by CLA$^+$ CD45RO$^+$ CD4$^+$ T cells in AD patients.[108] CLA$^+$ T_{reg} population from AD patients also express increased levels of OX40 compared to healthy controls and correlates with disease severity.[109,110]

IL-31 is a neuroimmune cytokine that was originally described as mainly produced by CLA$^+$ memory Th2 cells in AD,[64,111,112] with implications in pruritus, inflammation, fibrosis and epidermal barrier dysfunction.[113] Although there is an anti-IL31RA Mab (nemolizumab) in phase III for AD, the production of IL-31 and its relationship with the clinical status of the patients has not been characterized. A recent study has shown for the first time that in patients producing IL-31 by HDM-activated CLA$^+$ memory T cells, IL-31 directly correlated with patients' pruritus intensity, which was measured 24 h prior to sample collection, and plasma levels of periostin. The IL-31 response positively correlated with CCL27 plasma levels too (Figure 3), which is supported by the fact that stratum corneum CCL27 constitutes a biomarker of response to nemolizumab.[114] Additionally, it was suggested that plasma levels of HDM-specific IgE may stratify moderate-to-severe AD patients and hopefully be useful for identifying patients more probable to be responders for IL-31-directed therapies.[111] Interestingly, patients with elevated IgE levels (>1000 kU/L) display increased expression of IL-31RA on memory B cells,[115] supporting the association between IL-31 and IgE sensitization.

Th2 high and Th2 low endotypes have been hypothesized, supported by proteomic[116] and transcriptomic studies,[117] as well as differentiated responses to Th2-targeted therapies, and similarly to asthma. A recent coculture model defined the SEB-CLA$^+$ memory T-cell-IL-13 axis to functionally distinguish Th2 high and Th2 low responders within a clinically homogeneous adult moderate-to-severe AD population. Contrary to Th2 high group, where IL-13 response was associated with severity and Th2-related markers (CCL17, CCL26 and *S. aureus*-specific IgE), Th2 low group immune response skewed towards Th17, Th22, and Th1.[87]

3 | CONCLUSIONS

Translational research has bridged basic science with clinically relevant mechanisms of AD and provided a rationale for targeted therapies offering an integrated pathological view.[118] Current state of the art on the role played by circulating CLA$^+$ T cells in AD goes beyond their skin-homing capacities by clearly representing the Th2 immune axis dysregulation found in the disease. Although some

ILC2 cells express CLA, their role in adult moderate-to-severe AD is a complex matter, since ILC2 need to be activated by epithelial cytokines (alarmins) to induce Type 2 immune response and directed therapies against thymic stromal lymphopoietin (TSLP), IL-25, IL-33, and IL-1α have not demonstrated clinical efficacy.[62]

In the clinical context of the patients, CCL17, a chemoattractant of CLA^+ Th2 cells, has been postulated as the most reliable biomarker for pediatric and adult populations, as discussed above. As for the relationship between *S. aureus* and AD, CLA^+ T cells preferentially express specific TCR Vβ for *S. aureus* superantigens, such as SEB, leading to a broad cytokine-derived effector function (Th2, Th1, Th17, Th22), being IL-13 the most abundant Th2 cytokine produced. Regarding pruritus and IL-31, CLA^+ T cells are providing better understanding between clinical context of the patients and IL-31 production. From a therapeutic point of view, CLA^+ T cells are the subset of circulating memory T cells that reflects early effects of dupilumab on Th2 and Th22 responses in treated patients at Week 4.[102] All these different approaches suggest that CLA^+ T cells are at the core of AD pathogenesis. The study of SALT may provide a useful surrogate for investigating the immune-inflammatory cutaneous abnormalities present in AD.

AUTHOR CONTRIBUTIONS

Conceptualization: Luis F. Santamaria-Babí. Funding acquisition: Luis F. Santamaria-Babí, Ramon M. Pujol. Writing: Luis F. Santamaria-Babí, Lídia Sans-de San Nicolàs, Tali Czarnowicki, Mübeccel Akdis, Ramon M. Pujol, Daniel Lozano-Ojalvo, Donald Y. M. Leung, Emma Guttman-Yassky.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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