CLA + memory T cells in atopic dermatitis

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Abstract

CLA $^{+}$ memory T cells constitute a small subset of human memory T cells. Circulating skin-homing T cells participate in several aspects of atopic dermatitis, such as *Staphylococcus aureus* involvement in inflammation, 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 related to CLA $^{+}$ T cell response in patients. The function of CLA $^{+}$ T cells is closely related to 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. The goal of this review is to gather all this translational information of atopic dermatitis pathology.

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Short title**:** CLA^{+} T cells and atopic dermatitis

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Key words: atopic dermatitis, biomarker, CLA^+T cells, skin-homing, translational

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, 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] Other T-cell subsets such as type 2 innate lymphoid cells (ILC)2,[5]ILC3,[6] Vγ9Vδ2 T cells,[7] and $NKG2D^+$ $CD8^+$ T cells[8] express CLA. In addition, CLA is also expressed by regulatory T cells (T_{reg})[9] and effector memory B cells.[10] In human $CDR45RO^+$ T cells CLA is upregulated during the naïve to memory transition by fucosyltransferase VII.[11]

CLA has been shown to be induced by the effect of IL-12 on freshly generated Th1/Tc1 and Th2/Tc2 cells,[12] *ex vivo*in human Th2 cells,[13] as well as, by staphylococcal enterotoxin B (SEB).[14] At present, the functional implications in AD of that other T-cell types expressing CLA, besides the $CD45RO^+$ subset, have not been clarified.

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,[15,16] and together with other adhesion interactions (LFA-1/ICAM-1, and VLA-4/VCAM-1) and chemokines mediate transendothelial migration of CLA^+ T cells through the superficial vascular plexus.[17,18] The keratinocyte-derived chemokine CCL27/CTACK (T cell-attracting chemokine) binds to CCR10, that is preferentially

expressed on CLA^+ T cells.[19,20] CCL17/TARC (thymus and activation-regulated chemokine), one of the best biomarkers of AD,[21] binds to CCR4, which is preferentially expressed by $CD4^+$ CLA^+ memory T cells.[22] Moreover, CLA^+ memory Th2 cells from AD lesional skin selectively migrate to human skin grafts transplanted onto SCID mice in response to CCR4.[23]

Efalizumab, a LFA-1 targeting monoclonal antibody that blocks the LFA-1/ICAM-1 interaction, led to AD clinical improvement[24] and reduction of cutaneous CLA^+ memory T cells.[25] However, during treatment, patients presented with secondary CLA^+ lymphocytosis, that recirculated into the skin once treatment was interrupted, leading to disease exacerbation. There is normal T-cell recirculation/turnover between peripheral tissues (*e.g.* , skin) and blood. In that context, inflammatory cells can migrate back from the skin to the blood.[26] 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, implying that these circulating memory T cells might reflect cutaneous immune responses.[27]Consistently, it has been shown that CLA^+memory/effector T cells can be found in draining lymphatics of the skin.[28–30] 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),[31] suggests that circulating CLA^+ T cells may serve as cellular peripheral biomarkers in AD.[32]

CLA^+ T cells also represent activated immune cells that can migrate to various tissues and induce an inflammatory response. Similar type of cellular migration has been demonstrated in the circulation of patients with various chronic inflammatory diseases.[33–35] The frequency of allergen-specific T cells have been reported in 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.[33,36,37] 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.[35] Circulating T cells are highly active in polyallergic patients and express chemokine receptors for the migration to many different tissues.[38] 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.[39,40]

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.[41–43] 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, that 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.[44]

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 others, the existence of T cells with skin affinity and the ability to recognize skin-associated antigens.[45] 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 I).[46] 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. Circulating CLA^+ T cells respond to antigens, allergens, viruses, bacterial superantigens and drugs, with the common feature of being involved in the physiopathological mechanisms of distinct skin diseases such as dengue, leprosy, drug-induced allergic reactions, or alopecia areata, to name

a few (Table I). Additionally, their phenotype in circulation has been reported to correlate with the clinical activity and response to treatment of cutaneous diseases.[46]

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 identification of key disease pathways that are in the basis of those abnormalities such as CD4$^+$ memory T cell-derived cytokines IL-13, IL-4, IL-31 and IL-22.[47,48] CLA$^+$ T cells are abundant in lesional skin[31] and are related to different aspects of AD, including clinical features, response to treatment, and biomarkers (Figure 1).

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

Due to their homing/de-homing capacities between peripheral blood and skin, circulating CLA$^+$ T cells reflect cutaneous abnormalities present in AD lesions (Figure 1).[32]Circulating CD4$^+$ CLA$^+$ and CD8$^+$ CLA$^+$ T cells express increased levels of CD25, CD40 ligand, HLA-DR and ICOS,[33,49,50]and after being purified from blood these cells continue to proliferate spontaneously due to their *in vivo* activation phenotype in AD. Additionally, long term T-cell HLA-DR activation in skin-homing cells is increased in adults with AD compared to psoriasis patients or controls.[50] Circulating CD4$^+$ and CD8$^+$ CLA$^+$ T cells express the major type 2 cytokines IL-4, IL-5, and IL-13,[51] as well as, IL-9, IL-17A, IL-21 IL-22, IL-31, IFN-γ, TNF-α, and GM-CSF.[52–55]

CLA$^+$ T cells contribute to type 2 immune response by induction of IgE production by B cells and enhance eosinophil survival.[33,49,56] 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.[57,58]

Patients with AD showed increased frequencies of CLA expression and selective CLA$^+$ Th2/Tc2 and Th22/Tc22 expansion, accompanied by selective CLA$^+$ Th1/Tc1 reduction in blood.[53] 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,[59] '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.[50] Additionally, frequencies of IL-13-producing CLA$^+$ T cells and circulating CLA$^+$ T_{em} and T_{cm} cells significantly correlated with AD severity and total IgE levels in serum of AD patients, exemplifying how CLA$^+$ frequencies may reflect several disease aspects. The relatively easy access to CLA$^+$ T cells from peripheral blood provides less invasive, translational diagnostic approach, that might be particularly beneficial in certain populations, including children with AD, in whom skin sampling may pose a great challenge.[52] 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.[52] 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.[60] 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.[49] A recent study has shown that the T-cell receptor (TCR) repertoire of circulating allergen-specific CLA$^+$, but no CLA$^-$, T cells have a large overlap with this found in the infiltrated T cells of AD lesions for the same patient.[61]

Epigenetic modifications have been suggested as possible contributors to AD pathogenesis.[62,63] Examples include increased DNA methylation in the interleukin 4 receptor gene (*IL4R*) or reduced methylation in the thymic stromal lymphopoietin (*TSLP*) promoter, among others. Acevedo et al. showed that in AD patients, CLA$^+$ memory CD4$^+$ T cells are characterized by dysregulated epigenetic signatures affecting key

cytokine signaling pathways, such as reduced DNA methylation in the*IL13* promoter that may account for the augmented ability of this T-cell subset to produce IL-13.[31] Altogether these data suggest that CLA$^+$ T cells play a central role in the initiation and perpetuation of AD.[64]

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

S. aureus colonizes approximately 90% AD lesional and non-lesional skin compared to only 10% of healthy subjects[65] and is linked to AD flare up.[66] *S. aureus* is involved in microbial dysbiosis, skin barrier abnormalities and T cell-mediated inflammation.[67] It has been recently reported that*S. aureus*- colonized AD patients have a distinct phenotype and endotype with more severe disease.[68] SEB superantigen (Sag) is the most prevalent in AD[69] and it is associated with disease severity.[70] Application of SEB to intact AD skin induces dermatitis.[71] 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,[72,73] and an increased percentage of CLA$^+$ T cells bearing TCR Vβ for *S. aureus* Sags is found in children with AD.[74]

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 lesional T cells. This process is important in increasing the population of memory T cells that are capable of efficient extravasation to skin. These mechanisms may act to maintain 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, IL-22, CCL17 and CCL22), with IL-13 as one of the highest produced Th2 cytokine and the only one 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).[75] α-toxin 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.[76]

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.[21,77] Over 100 different markers have been suggested as biomarkers in AD. The most reliable biomarker reported is serum CCL17.[21]

The CLA$^+$ T cells and CCL17 functions are related mechanisms in AD. CCR4 is a receptor for CCL17 preferentially expressed on circulating CLA$^+$ CD4$^+$ memory T cells[22] and T_{reg},[78]and CLA$^+$ memory Th2 cells from AD patients selectively migrate to human skin grafts transplanted onto SCID mice in response to CCR4.[23] Recent clinical data in children and adults highlight CCL17 as a potential biomarker. Two independent pediatric studies have shown that increased levels of skin CCL17 may predict AD development in infancy.[79,80] It may be hypothesized that since children present a preferential Th2 response in CLA$^+$ T cells,[4] the link between skin CCL17 and AD development in these population, is in line with the pathological role of CLA$^+$ T cells in AD. In addition, in adults a recent phase 1b study have shown that the oral CCR4-antagonist RPT193 led to clinical improvement in moderate-to-severe AD.[81] On the other hand, the CCL27 that is a CLA$^+$ T cells attracting chemokine, has been shown to be increased in the stratum corneum and associated with disease severity in pediatric AD[82]. In adults, stratum corneum CCL27 also constitutes a biomarker of response to nemolizumab.[83]

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.[84]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,[85] a fact that limits its use as a biomarker.

Another important feature of a biomarker is its ability to predict and monitor therapeutic responses. 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 that while their relative proportion remains unchanged, there was 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 CLA^+, but not CLA^-, $CD4^+$ T cells, supporting CLA^+ T-cell responses as a surrogate measure to dupilumab efficacy.[86,87]

As mentioned above, another consideration is the accessibility of (obtaining) 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.[88] The fact that CLA^+ T cells are effortlessly extracted from peripheral blood tests puts them under the category of minimally invasive biomarkers,[21] and reinforces their potential as disease biomarkers in AD.

The OX40-OX40L interaction is involved in long-term and optimal cell activation of CD4 T cells[89] and OX4O signaling favors expansion and survival of Th2 cells.[90] OX40 is also highly expressed by CLA^+ $CD45RO^+CD4^+$ T cells in AD patients.[91] The OX40-OX40L axis has recently attracted attention in AD due to the improvements shown in AD patients for both an anti-OX40 depleting antibody (KHK4083)[92] and a non-depleting monoclonal antibody (Mab) (amlitelimab) that binds to OX40L present on antigen presenting cells (SAR445229).[93]

IL-31 is a neuroimmune cytokine that was originally described as mainly produced by CLA^+ memory T cells in AD.[94,95] Although there is an anti-IL31RA Mab 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 AD patients producing IL-31 by HDM-activated CLA^+ memory T cells, IL-31 directly correlated with patients' pruritus intensity and plasma levels of CCL27 and periostin (Figure 3). 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.[96]

Supported by proteomic[97] and transcriptomic studies,[98] as well as, differentiated responses to Th2-targeted therapies, and similarly to asthma, Th2 high and Th2 low endotypes have been hypothesized. 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, Th2 low group mainly produced IL-17A, IL-22 and IFN-γ and IL-13 response did not correlate with EASI, plasma levels of CCL17 and*S. aureus* -specific IgE, and CCL26 mRNA expression from cutaneous lesions.[75]

Conclusions

Translational research has bridged basic science with clinically relevant mechanisms of AD, and provided a rational for targeted therapies in AD offering an integrated pathological view.[99] Current state of the art on the role played by circulating CLA^+ T cells in AD goes beyond their skin-homing capacities and describe an integrative perspective of AD pathophysiology. The abnormal Th2 responses found in AD is clearly represented by CLA^+ T cells and integrated in disease pathology. 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 TLSP, IL-25, IL-33 and IL-1α have not demonstrated clinical efficacy.[48]

In the clinical context of the patients, to highlight that in pediatric patients CCL17 is a biomarker of AD severity progression where IL-4 and IL-13 response is mainly present in CLA^+, but not CLA^-, $CD4^+$ T cells, and in adults CCL17 is one of the best biomarkers for AD. CCL17 mechanistically relates to CLA^+ Th2

cells, since it binds to CCR4, which is preferentially expressed on skin-homing T cells. 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.[86] All these different perspectives suggest that CLA^+ T cells are in the core of AD pathogenesis, probably since studying SALT may provide a useful surrogate for investigating the immune-inflammatory cutaneous abnormalities present in AD.

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Box. Bullet points (future research perspective)

- Explore gut to skin homing in AD pathophysiology.
- Better understand the role of CLA^- memory T cells in extracutaneous AD comorbidities.
- CLA^+ T cell effector function in AD heterogeneity and in the context of response to treatments.
- CLA^+ T cells response and epithelial barrier hypothesis in AD.

Table I. Skin-associated lymphoid tissues (SALT) and human skin diseases have a close relationship with CLA^+ T cell biology.

PROPERTIES OF SALT	CLA^+ T CELL FEATURES
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 proc
Immune recognition of antigen in the skin.	Preferentially respond to antigens related to skin.
HUMAN SKIN DISEASES BESIDES AD	**CLA^+ T CELL INVOLVEMENT**
Allergic contact dermatitis	Response to nickel, cobalt, and chromium metal allergy.[10
Alopecia areata	Th2/Tc2 activation.[101]
Drug-induced allergic reactions	Response to drugs.[102]
Guttate psoriasis	*Streptococcus pyogenes* induces Th17 response.[103]
Herpes Simplex	$CD8^+$ T anti-viral response.[104]
Leprosy	Antigen-specific response.[105]
Melanoma	Skin metastasis and response to therapy.[106]
Papuloerythroderma	Higher proportion than CLA^- of IL-4, IL-13, IL-22 and IL
Plaque Psoriasis	Response to *Streptococcus pyogenes* and relation with clin
Rosacea	Response to demodex.[109]
Skin dengue infection	Response to Dengue.[110]
Vitiligo	Response to autoantigens.[111]

AD, atopic dermatitis; CLA, cutaneous lymphocyte-associated antigen; SALT, skin-associated lymphoid tissues.

Figure legends

Figure 1. CLA^+ memory T cells in the pathological mechanisms of AD. The memory phenotype of CLA^+ T cells together with their selective migration to skin involve these cells in AD pathological mechanisms. By virtue of their de-homing capacity, circulating CLA^+ T cells reflect cutaneous abnormalities present in AD lesions, including*S. aureus* infection, 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. AD, atopic dermatitis; 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.

Figure 2. SEB, IL-13, and CCL17 mechanisms meet in CLA$^+$ T cells 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 are found, and an IL-13 dominated transcriptional inflammatory signature is present. CLA$^+$ T cells in AD present an epigenetic alteration for IL-13. SEB-induced IL-13 in CLA$^+$ T cells 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 also correlates with CCL26 mRNA expression in lesional skin. AD, atopic dermatitis; APC, antigen presenting cell; CLA, cutaneous lymphocyte-associated antigen; EASI, eczema area and severity index; MHC-II, major histocompatibility complex class II; *S. aureus, Staphylococcus aureus* ; SEB, staphylococcal enterotoxin B; TCR, T-cell receptor.

Figure 3. HDM relates specific CLA$^+$ T cell response with pruritus and IL-31. 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 lymphocyte in AD lesions and major producers of IL-31. HDM-induced IL-31 by circulating CLA$^+$ T cells correlated with patient´s pruritus, and plasma levels of periostin, in patients with HDM-specific IgE. On the other hand, plasma levels of the keratinocyte-derived CCL27, a ligand for CCR10 that is preferentially expressed by CLA$^+$ T cells, correlates with HDM-induced IL-31. Interestingly, CCL27 in the stratum corneum is a biomarker of response to anti-IL31RA therapy in AD. AD, atopic dermatitis; APC, antigen presenting cell; CLA, cutaneous lymphocyte-associated antigen; HDM, house dust mite; MHC-II, major histocompatibility complex class II; TCR, T-cell receptor.

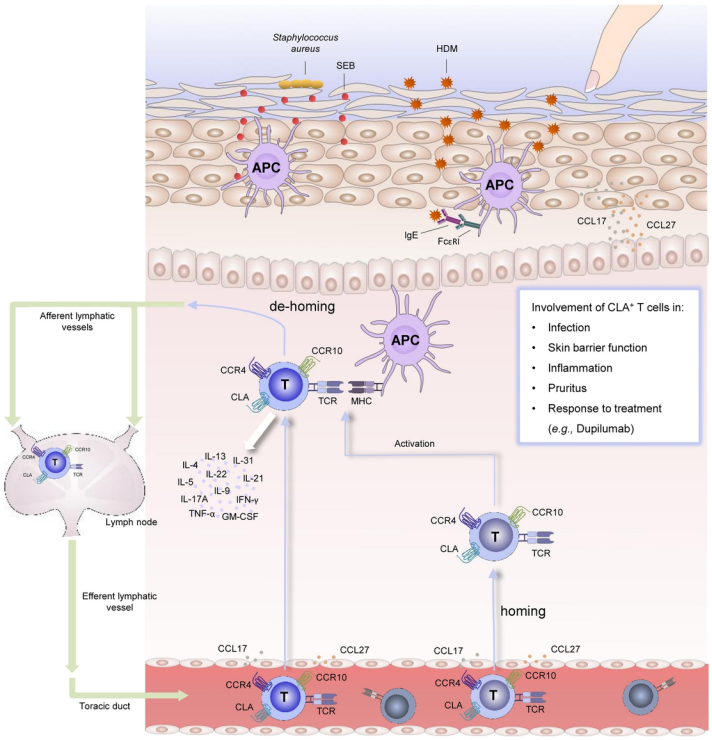

Figure 1_Sans-de San Nicolàs et al.

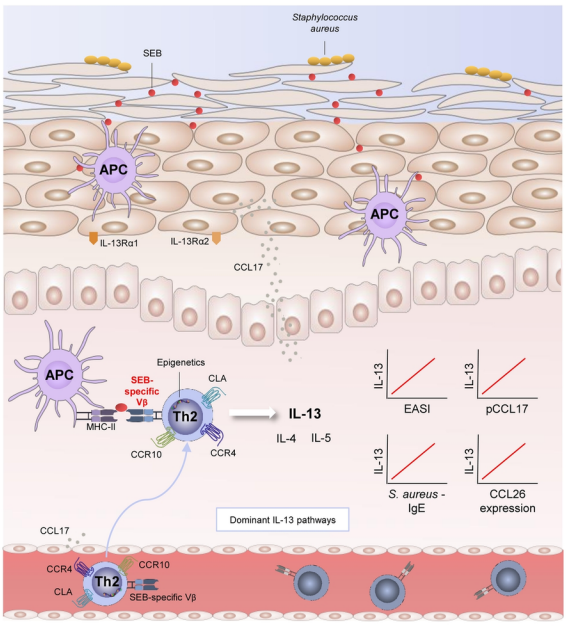

Figure 2_Sans-de San Nicolàs et al.

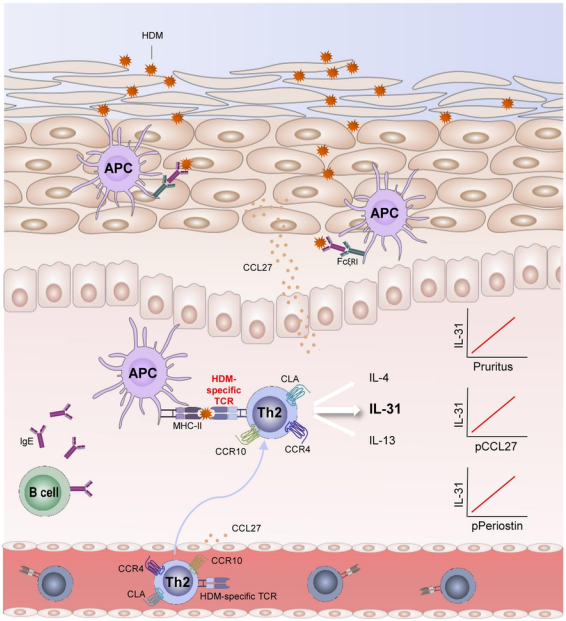

Figure 3_Sans-de San Nicolàs et al.