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T-cell subsets in the skin and their role in inflammatory skin disorders

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T lymphocytes (T-cells) are major players of the adaptive immune response. Naive T-cells are primed in the presence of cytokines, leading to polarization into distinct T-cell subsets with specific functions. These subsets are classified based on their T-cell receptor profile, expression of transcription factors, surface cytokine and chemokine receptors, and their cytokine production, which together determine their specific function. This review provides an overview of the various T-cell subsets and their function in several inflammatory skin disorders ranging from allergic inflammation to skin tumors. Moreover, we highlight similarities of T-cell responses across different skin disorders, demonstrating the presence of similar and opposing functions for the different T-cell subsets. Finally, we discuss the effects of currently available and promising therapeutic approaches to harness T-cells in inflammatory skin diseases for which efficacy next to unwanted side-effects provide new insights into the pathophysiology of skin disorders.

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VII Main text

1 Introduction

The human skin is a multifunctional organ that is essential for systemic homeostasis. Epidermal barrier formation provides a first line of defense against exogenous threats, including microbial and physical agents and regulates the water loss. Additionally, it actively contributes to immune responses as a sentinel organ via the release of cytokines and chemokines that alarm immune cells in case of skin damage or infection. Epidermal keratinocytes are known to produce thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33 in response to environmental signals, which activates innate lymphoid cells (ILCs), T-lymphocytes (T-cells), mast cells (MCs) and eosinophils.

This review focusses on the various cutaneous T-cell subsets and their role in inflammatory skin disorders, and skin tumors. T-cell subsets orchestrate disease pathophysiology by the production of particular cytokines, which in turn affects interactions with other immune cells, such as B-cells, eosinophils, neutrophils, and MCs. Therefore, these adaptive immune responses play a central role in the many inflammatory skin diseases, but also in infections and skin cancer. Additionally, currently available T-cell targeted therapies and future directions will be addressed.

2 Role of T-cell subsets and innate lymphoid cells in healthy skin

2.1 Conventional and unconventional T-cells

Conventional T-cells express a highly diverse T-cell receptor (TCR) repertoire, consisting of α and β-chains, which determine antigen specificity. They are further classified into $CD4^+$ and $CD8^+$ T-cells, depending on respective co-receptor expression. Upon recognition of cognate antigens, naive T-cells from both lineages differentiate into effector T-cells that exert specific functions depending on their differentiation program. $CD4^+$ T helper (Th) subsets are primarily classified based on their master transcription factor profile and cytokine production, including T-BET, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α for Th1, GATA-3, IL-4 and IL-13 for Th2, IRF 4 and IL-9 for Th9, ROR$\gamma\tau$, IL-17a and IL-17F for Th17, AHR and IL-22 for Th22, and BCL-6 and IL-21 for T follicular helper (Tfh) cells (**Figure 1**). Another characteristic Th-cell feature is distinct expression of chemokine receptors, which enable T-cell recruitment to tissues. Naive T-cells express CXCR4

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and CCR7, which mediate spatial accumulation with dendritic cells (DCs) in lymphoid tissues. Upon activation and polarization, CXCR4 and CCR7 are downregulated, while the expression of other chemokine receptors is upregulated. For instance, co-expression of CXCR3 and CCR5 is upregulated by Th1 cells, while CCR3 and CCR4 are predominantly expressed on activated Th2 cells (**Table 1**). Canonical $CD4^+$ T-cell subsets also include *FOXP3*-expressing regulatory T-cells (Tregs) that are mostly thymus-derived but may also be induced in the periphery under specific circumstances, and exert suppressive functions by IL-10 and transforming growth factor (TGF)-β. For $CD8^+$ cytotoxic T-cells (Tc) a similar, albeit less demarcated classification exists with Tc1, Tc2, Tc9, Tc17, Tc22 (Reviewed in (1,2)) (**Figure 1, Table 1**). Importantly, a rapidly growing body of single-cell sequencing and epigenetic data demonstrates substantial heterogeneity and plasticity among T-cell subsets (3,4), suggesting that current T-cell subset working models do not reflect the complete T-cell differentiation complexity.

A proportion of effector $CD4^+$ and $CD8^+$ T-cells becomes long-lived by differentiating into self-renewing memory T-cells. Central memory T cells (T_{CM}) circulate in blood and traffic through lymphoid tissues, while effector memory T-cells (T_{EM}) enter and patrol peripheral tissues, including skin (5). It has become clear that a significant part of tissue T-cells can become resident (6). Tissue-resident memory T-cells (T_{RM}) provide local surveillance and are retained in tissues (7,8).

Besides conventional T-cells, several unconventional T-cell subsets have been described such as γδ T-cells, natural killer (NK)T-cells, and Mucosal Associated Invariant T (MAIT) cells. These less abundant T-cell subsets have in common that they express semi-invariant TCRs, recognize specific (often non-peptide) antigen classes, possess innate-like properties, and are enriched in barrier tissues where they play a role as pathogen sentinels (9).

2.2 T-cells in the skin

Under steady state conditions, the human skin harbors billions of T-cells, largely composed of resident cells next to recirculating memory T-cells (8,10,11). In the skin, Langerhans cells and DCs are the most important professional antigen-presenting cells (APCs) which act as gate keepers, presenting captured antigens on major histocompatibility complex (MHC) proteins to naive T-cells. The latter takes place in skin draining lymph nodes, after which T-cells become activated and primed for skin-homing, orchestrated by specific chemokine

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receptors (CCR4, CCR10, and CCR8) (12,13) next to cutaneous lymphocyte antigen (CLA), a ligand for E- and P-selectin, and a glycovariant of P-selectin glycoprotein ligand-1 (14) (**Figure 2A**). Subsequently, T-cells can activate various differentiation programs depending on their surroundings. After T-cells encounter specific antigens, this can lead to clonal proliferation, cytokine release and activation of other immune cells (e.g. B-cells) or cells in their local environment (e.g. keratinocytes). During inflammation, T-cell migration into the skin is more permissive and enhanced via local pro-inflammatory chemokine and cytokine production, such as recruitment of $CXCR3^+$ T-cells by local CXCL9, CXCL10, and CXCL11 production.

In the skin, a part of the recruited T-cells further develops into T_{RM}. Markers that are most widely used to identify T_{RM} in the skin are CD69, CD103 and CD49a. Expression of CD69 is important for tissue retention as it antagonizes S1PR1, required for migration of T-cells out of tissues (15). However, CD69 expression is not an absolute requirement for T_{RM} maintenance as also $CD69^-$ T_{RM} populations have been described. In healthy human skin, most of the T_{RM} in the dermis are $CD4^+CD69^+CD103^-$ cells, while the epidermis contains a mixed population of $CD4^+$ and $CD8^+$ $CD69^+CD103^+$ T_{RM} (10), with $CD8^+CD49a^+$ T-cells poised for cytotoxic function (16). T_{RM} development is presumed to be driven by antigen exposure, together with cytokines and chemokines in the local tissue environment. TGF-β has been shown to drive T_{RM} generation (by downregulation of the transcription factors Eomes and T-bet), and to induce CD103 expression. Recent studies in mice suggest that T_{RM} can sustain themselves in the skin via local proliferation (17), and that long-term survival of T_{RM} depends on IL-15 and lipid uptake (18–20). In general, T_{RM} exhibit an elevated inflammatory cytokine and cytotoxicity-associated transcriptional profile compared with circulating memory T-cells, suggesting a poised state for rapid effector function upon activation (21). Additionally, $CD4^+$ and $CD8^+$ T_{RM} also express multiple inhibitory surface molecules, indicating that T-cell function is tightly regulated (21). T_{RM} from different tissues share a core signature, yet tissue-specific adaptations and inter-tissue-heterogeneity exists (21). In steady state, skin T_{RM} are thought to play a role in tissue homeostasis, while upon local (re)infection or under chronic inflammatory conditions, T_{RM} rapidly accumulate in the skin, produce inflammatory cytokines (e.g. IFN-γ, IL-22, IL-17) and can exert cytotoxic functions (16,22–24). Also, resident Tregs are located in the skin. In murine skin, Tregs have been demonstrated to facilitate wound healing and modulate hair follicle stem cells (25,26) and also in humans, cutaneous Tregs display a tissue repair signature (27).

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In mice, T-cells that are not restricted to classical MHCs (γδ T-cells, MAIT-cells, and CD1-reactive T-cells) play an important role in skin immunity and homeostasis (reviewed in (28)). In humans, these T-cell populations (especially the γδ T-cells) are less abundant and therefore their role is less clear.

2.3 Innate lymphoid cells

In mice and men resident ILCs contribute to skin homeostasis and immunity via cytokine secretion and regulation of innate and adaptive immune cells. Despite their lack of antigen-specific TCRs, ILCs show parallels with conventional T-cell subsets, and therefore, ILCs are discussed briefly. ILCs are mainly present at barrier surfaces, which reflects their role as first line immune regulators. Under homeostatic conditions ILCs reside in low numbers in the dermis and are involved in tissue repair. They rapidly respond to signals in the microenvironment via cytokine production (reviewed in (29,30)). Several subsets of ILCs are characterized (reviewed in (29)) (**Table 1**): Type 1 ILCs (ILC1) are the innate variant of Th1, whereas NK cells are the innate equivalent of Tc1, which are present in the dermis, intestines, liver and lung. ILC1s are activated by IL-12 and IL-18, and produce IFN-γ. As a response to microbial exposure, these cells increase in number and initiate a pathogen-specific immune response (31) (reviewed in (32)). Type 2 ILCs (ILC2s) are the innate equivalents of Th2 and the most abundant ILC subtype in the skin, where they reside in close proximity of MCs and keratinocytes, and respond to IL-25, IL-33, TSLP or prostaglandin (33,34). They are an important source of IL-5, IL-13, and also produce amphiregulin (a cell growth signal, survival, migration and immune modulation) (35). Due to their mediator profile, ILC2 act as early responders in allergic inflammation. Lymphoid tissue inducer cells (Lti) represent the Th17 cells and type 3 ILCs (ILC3s) correspond to Th22 (**Table 1**). ILC3s are activated by IL-1β, IL-23, and aryl hydrocarbon receptor ligands, and produce IL-17A, IL-17F, IL-22, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF).

3 The role of T-cells in inflammatory skin diseases including T-cell therapies

3.1 Allergic inflammation

External allergens can initiate allergic sensitization with a Th2-skewed T cell response and immunoglobulin E (IgE) antibody-production, resulting in acute and chronic cutaneous inflammation. Upon exogenous allergen

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exposure, APCs migrate to local lymph nodes to prime naive T-cells which differentiate in the presence of IL-4 into allergen-specific Th2-cells. Th2-cells induce an IgE class switch of B-cells, which leads to MC sensitization. In acute Type-I hypersensitivity reactions, allergen re-exposure induces rapid MC degranulation. In the late phase response, activated antigen-specific Th2-cells produce pro-inflammatory cytokines (**Figure 2B**). While IL-4, IL-13 and histamine can contribute to an impaired skin barrier function (36–38), IL-5 and IL-9, produced by Th9-cells, attract eosinophils. IL-13 regulates inflammation via stimulation of IgE-producing B-cell proliferation, fibrosis, and recruitment of inflammatory cells and changes in the skin microbiome (38). IL-31 elicits pruritus by binding to its receptors on sensory nerves in the skin. Additionally, ILC2s produce IL-5 and IL-13 in response to prostaglandin and leukotrienes secreted by MCs or IL-33 and TSLP from keratinocytes (39). Recently, the "barrier hypothesis" was introduced, suggesting that increased epithelial barrier-damage can be related to industrialization, urbanization and lifestyle changes. This implies that not only allergens, but also infections, pollutants and other environmental triggers impact allergic inflammation (40).

3.2 Atopic dermatitis

Atopic dermatitis (AD) is a common skin disease affecting up to 20% of children and approximately 5% of adults (41). It is characterized by impaired skin barrier function and inflammation of the skin resulting in pruritus and formation of eczematous areas. The disease course of AD can be affected by external factors, like allergens (e.g. house dust mites), resulting in IgE-mediated allergic skin inflammation, as described above. Many patients with AD exhibit chronic skin inflammation in the absence of sensitization to external allergens, pointing out the importance of endogenous factors which can contribute to persistent inflammation via T-cell activation. Therefore, both local as well as systemic immune mechanisms can act as underlying causes.

A hallmark in AD is a marked T-cell influx in the epidermis at the site of the itchy eczema (42). Notably, healthy skin contains twice as many T-cells and atopic skin even thrice as many as peripheral blood (43). This implies that although research on cutaneous T-cells is technically more challenging than on T-cells in peripheral blood, the analysis of peripheral blood T-cells may not fully represent the immunopathology impact of T-cells in AD. The majority of T-cells are $CD4^+$ with a dynamic Th-subset pattern: from Th2 and ILC2s in more acute, towards Th1/Th2 in more chronic inflammatory AD conditions (44) (**Figure 2C**). Keratinocyte apoptosis in eczema lesions is linked to IFN-ɣ release and FAS expression by epidermal $CD4^+$ T-cells (45). More recent studies also describe the presence of IL-17, IL-21 and IL-22 releasing $CD4^+$ T-cells in atopic skin (46,47),

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with a more profound Th17-profile in the Asian population (48). IL-22 induces keratinocyte proliferation and epidermal thickening in AD. Although $CD8^+$ T-cells comprise up to 30% of the skin T-cell population in AD, mostly in the epidermis, knowledge on this population is scarce. Skin $CD8^+$ T-cells in AD are a potent source of IL-13, IFN-ɣ and IL-22 (49), suggesting a pathogenic contribution to inflammation in AD.

Skin T-cell activation is achieved in multiple ways: by release of innate type cytokines, as well as antigens by epidermal cells. It has also been shown that, although the skin T-cell population is polyclonal, allergen-specific long-lived T-cell clones can be obtained from skin (50). In addition, skin T-cell reactivity has been demonstrated for microbial and autoantigens (51). Patients with AD can have a Th2-induced decreased production of antimicrobial peptide (AMP), leading to an increased risk for colonization with *Staphylococcus aureus* or other pathogens (49). During cutaneous herpes simplex virus 1 infections, nociceptive sensory neurons reduce neutrophil skin infiltration, promoting the induction of an antiviral CD8 T-cell response (52).

The characteristic increase in T-cell number in skin can be due to local proliferation, and selective T-cell skin homing. More than 90% of the skin T-cells express CLA, which is a selective adhesion molecule (53). In addition, also CCR10 and CCR4 chemokine receptors are expressed on the majority of skin-dwelling T-cells. The ligands for CCR4, CCL17/TARC, and for CCR17, CCL27/CTACK are specifically increased in the blood of AD patients (54,55). The CCL17/TARC serum concentration is related to the AD severity within individual patients and is an informative biomarker in AD (56).

Several pharmacological interventions indicate the crucial role of T-cells in AD. For example, cyclosporine (CsA), which acts on T-cells specifically by blocking calcineurin activity, is effective in a large subgroup of severe AD-patients (57). Recently, treatment with antibodies, specifically targeting immune players, provided further insight in the role of T-cells and their products (**Table 2**). Regarding the role of type 2 responses in AD, it was found that blocking IL-5 by mepolizumab does not improve AD (58). The effect of blocking IgE by anti-IgE (omalizumab) is still inconclusive (59), especially because high serum levels of IgE in AD may limit the effectiveness of omalizumab. A profound clinical effect on AD is observed by dupilumab-mediated blocking of IL-4Rα, which prevents binding of IL-4 and IL-13, indicative for their crucial role in AD (60–62). Depletion or inhibition of IL-13 has modest to sustained effects on AD (63–65). Binding of cytokines, such as IL-4 and IL-13, results in signaling via Janus kinases (JAKs). JAK1/JAK3 inhibitors have also been proven to be efficacious in AD (66–70). Reduction in pruritus was obtained using a monoclonal antibody against IL-31 (71). As previously

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stated, in some AD patients also a local Th17 population is described. However, targeting IL-17 did not have a significant effect on AD (72).

For improved personalized treatment of AD, disease endotyping can be an effective approach. Different immunologic backgrounds that underlie AD became clear via cluster analysis, which identified 4 serum biomarker-based clusters; "skin-homing chemokines/IL-1R1-dominant", "Th1/Th2/Th17-dominant", "Th2/Th22/PARC-dominant", and a "Th2/eosinophil" cluster (73). Another endotype that has been proposed is the presence of autoreactive T-cells and IgE autoantibodies directed to autoantigens in the skin (74,75). Due to chronic skin inflammation and skin damage, epitope spreading may activate autoimmune processes and bystander activation of (autoreactive) T-cells, which can activate B cells to produce autoreactive IgE antibodies, resulting in an IgE-mediated autoreactive response (76,77). However, to date it is unclear whether the presence of autoreactive T-cells and IgE autoantibodies form a distinct cluster, arguing for more research into its clinical relevance.

In conclusion, marked T-cell activation in AD is observed systemically and locally. Although the T-cell phenotype is dynamic, Th2-cell functions seem dominant in this pathology.

3.3 Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by scaly erythematous plaques (78). Psoriasis affects approximately 2–4% of the population and may also involve the joints. Th17, Th1-cells and $CD8^+$ T-cells (Tc17) are the main players in disease pathophysiology, and also MAIT-cells may act as an alternative source of IL-17A in psoriasis affected skin (79). IL-17 and IL-22 modulate gene expression in keratinocytes. IL-17 was shown to upregulate the expression of immune cell chemo-attractants that contribute to psoriasis pathogenesis and IL-22 regulates terminal keratinocyte differentiation and epidermal thickening (78). Monoclonal antibodies that target IL-17 (**Table 2**) were shown to be effective for controlling psoriasis (80–83). Additionally, TNF-inhibitors (**Table 2**) can improve the symptoms (84), although, T_{RM} cells still reside in recovered skin lesions.

ILC3s are increased both in the skin and blood of patients with psoriasis (35,85,86), and ILC3 numbers correlate with disease severity (79). IL-23 is produced by activated DCs, macrophages, or monocytes, but also by ILCs and γδ T-cells. IL-23 is also important for the maintenance and expansion of IL-17A-producing T-cells.

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IL-12, also produced by DCs, and a close family member of IL-23 is crucial for NK cell activation and Th1-cell differentiation (**Figure 2D**). The contribution of IL-12 and IL-23 to psoriasis pathophysiology is reflected by the efficacy of biological antagonists, of which several have been approved to treat psoriasis (87–90) (**Table 2**).

3.4 Chronic spontaneous urticaria

In the skin of chronic spontaneous urticaria (CSU) patients, lesions are infiltrated with T-cells that reside near MCs. CSU is further characterized by increased expression of IL-33, IL-25 and TSLP, which can trigger MCs, leading to vascular leakage and an inflammatory response (91). Around 50% of CSU patients have a positive autologous serum skin test ($ASST^+$) (reviewed in (92)). IgE or IgG autoantibodies against thyroid antigens, double stranded DNA or IL-24, have been detected and are associated with disease activity and with predictive relevance (93–96). IgG autoantibodies and autoreactive $CD4^+$ T-cells against FcεRIα have also been identified in peripheral blood and were inversely correlated to a Th1-cytokine response, suggesting that IFN-γ is present in early stages and auto-reactivity develops in later stages of CSU (97). The presence of atopy and/or a positive response to serum auto-reactivity was linked with differences in Th1, Th2, Th17 and Th22 cytokine expression patterns, suggesting that several mechanisms underlie the emergence of urticaria (98). Expression of IFN-γ, IL-2 and IL-21 is associated with auto-reactivity (98). These cytokines are regulated by the JAK/STAT pathway and may thus be of importance for therapeutic approaches (**Table 2**). Targeting IgE with omalizumab or ligelizumab are highly effective treatments (99,100). Several off-label treatments of CSU patients with dupilumab, as well as IL-5 receptor antibodies and IL-5 antibodies have been effective, indicating a role of Th2 cell products in CSU (reviewed in (101)).

Th17, Tc17 and MCs produce IL-17A. Increased numbers of Tc1 and Tc17 were observed in $ASST^+$ compared to $ASST^-$ patients and healthy controls (102). Also, elevated frequencies of Th17 and IL-17 serum levels have been associated with disease severity, which makes IL-17 a potential target in CSU. In response to secukinumab, an anti-IL-17A antibody, a reduced disease activity was found in patients with CSU (103). Although, some studies showed no difference in IL-17 serum levels or even lower numbers of Th17-cells compared to healthy controls (102,104). Finally, reduced numbers of peripheral blood Tregs were found in chronic urticaria patients, yet their specific function in CSU still warrants further investigation (104).

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3.5 Connective Tissue Diseases

Connective tissue diseases include several disorders, such as rheumatoid arthritis, scleroderma, lupus, and dermatomyositis. Patients present multi-organ involvement, including joint pain, hematologic aberrations, kidney dysfunction, and often skin signs.

In patients with connective tissue disease, reduced numbers of peripheral blood Tregs were found compared with healthy controls. Frequencies of Tregs inversely correlated with disease activity and the presence of autoantibodies (105). Presence of anti-melanoma differentiation-associated gene 5 (MDA5, a cytoplasmic RNA sensor) autoantibodies and a high age at disease onset are factors for poor prognosis in patients with polymyositis and dermatomyositis with interstitial lung disease (106). Serum levels of IFN-α and ferritin were increased in the anti-MDA5 antibody positive patients with dermatomyositis and can be used as biomarkers (107). In response to rituximab therapy (monoclonal anti-CD20 antibody), these patients improved skin rash and interstitial lung disease (108). Nintedanib inhibits both nonreceptor tyrosine kinases and receptor tyrosine kinases, which reduced progression of interstitial lung disease in patients with systemic sclerosis (109). Additionally, JAK inhibitors have been suggested as an alternative treatment for dermatomyositis (110), as effects of IFNs are mediated through the JAK/STAT pathway. In patients with dermatomyositis, T-cell numbers were decreased, which was associated with interstitial lung disease (111).

In the pathophysiology of connective tissue diseases, an imbalance of TCR-signaling and reduced expression of FoxP3 may underlie disease pathophysiology. Decreased tolerance resulting from lower Treg numbers might be central, pinpointing Treg activation as an interesting therapeutic approach.

3.6 Other inflammatory skin diseases

In cutaneous lichen planus, key inflammatory players are IFN-γ and IL-21 (112). IL-21 is produced by $CD4^+$ Tfh and NKT cells. Upon binding to its receptor (IL-21R), the JAK(1/3)/STAT(3/1/5)-pathway is activated, which augments T-bet and STAT4 expression in T-cells and IFN-γ production. JAK inhibitors, such as tofacitinib, can be an effective therapy to treat lichen planus (112,113).

In contrast to connective diseases or other inflammatory skin diseases, the causative cutaneous antigens of bullous pemphigoid are well described. Autoreactive IgG or IgE autoantibodies to the antigens BP180 or

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BP230 induce pruritic eczematous or urticarial lesions and subepidermal blister formation, mainly in elderly patients (114–116). In addition, Th17-cells and autoreactive Th1/Th2-cells have been observed including a mixed spectrum of cytokines, such as IL-17, IFN-γ and IL-5 (117). Moreover, Th2 cytokines were found in blisters, which point to an additional role of Th2-cells, a fact that is further substantiated by the identification of anti-BP180/230 IgE autoantibodies (118,119).

Alopecia areata is a chronic, relapsing, skin disease leading to patchy hair loss that can reversibly affect small areas of the scalp or trunk, but can also progress to large, therapy resistant areas with complete hair loss. $CD8^+$ T-cells are regarded as main causative cells in alopecia areata, however, a recent murine study identified a mixed profile of both $CD4^+$ and $CD8^+$ T-cells (120). Classical treatments include topic or systemic corticosteroids, but recently JAK1/3 inhibition using tofacitinib and ruxolitinib proved to be a highly effective treatment (121).

Vitiligo is a patchy, progressive depigmentation disorder of the skin. There are several hypotheses on vitiligo pathogenesis, of which a $CD8^+$ T-cell-mediated destruction of melanocytes (122). In a murine model, CXCL10 neutralization improved the disease resulting in renewed pigmentation, suggestive for a critical role of CXCL10 in vitiligo (123). Recently, evidence for Th9-cells was observed by flow cytometry (124). In a phase 2 trial, treatment with ruxolitinib cream showed renewed pigmentation of the lesions, which implies an effective treatment approach for vitiligo (125).

3.7 Melanoma and non-melanoma skin cancers

Skin cancer can take many forms and shapes both with respect to pathophysiology and prognosis. Skin cancers can be broadly divided into melanoma and non-melanoma skin cancers (NMSCs), represented by basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSCs are responsible for only a small fraction of mortality. In contrast, melanoma, resulting from uncontrolled growth of melanocytes, represents only a minority of the skin cancer cases yet is responsible for the majority of skin cancer-related deaths (126,127). There is compelling evidence that melanoma can be killed by T-cells. Over 50 years ago, dermal lymphocyte reactions were described at early stages of primary melanoma growth (128). Moreover, clonal T-cell expansion is observed in regressing melanoma (129,130) while T-cell infiltration in stable and even progressive disease, is correlated to prolonged survival and lower risk of metastasis (131,132).

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Characterization of these T-cells has resulted in identification of melanoma-associated antigens and neoantigens that allow T-cells to selectively kill melanoma cells (133,134). Specifically, $CD8^+$ T-cells can recognize antigen-derived peptides presented via MHC-I on melanoma cell surface after which they can exert their cytotoxic function using Fas Ligand, perforin and granzyme B, and cytokines such as IFN-γ and TNF-α (**Figure 2E**) (135). Additionally, IFN-γ-secreting Th1-cells can recognize antigen-derived peptides in MHC-II and aid $CD8^+$ T-cell activation. These $CD4^+$ T-cells can also kill melanoma cells that show expression of MHC-II and their cognate antigen (136,137), using IFN-γ, perforin and granzyme B, rather than Fas Ligand, as their weapon of choice (138,139). The important role of Th1-cells in rejecting melanoma cells, independent of MHC-II expression, is further evidenced by their ability to stimulate macrophage-mediated cytotoxicity (139). The role of Th9 and Th17 subsets in melanoma is increasingly explored. These Th-subsets merit attention as they can exert direct cytotoxic functions through production of cytokines and granzyme B (140–143). Th9-cells, similar to Th1-cells, exert multiple supportive antitumor activities, including recruitment and/or activation of innate immune cells like MCs (140), DCs (141) and NK cells (144). Th17-cells can also facilitate $CD8^+$ T-cell recruitment, yet can also promote angiogenesis and tumor proliferation, and even adopt a Treg-phenotype, thereby opposing tumor rejection (145). $CD4^+CD25^{high}Foxp3^+$ Tregs represent a predictive marker for tumors that are escaping immune-mediated killing as they possess a multitude of T-cell suppressive mechanisms, e.g. TGF-β production (146,147).

Unconventional T-cells remain less well studied. γδ T-cells that are attracted to melanoma via the CCR2/CCL2-pathway have anti-tumor traits (145). These γδ T-cells can recognize tumor-specific ligands neglected by conventional αβ T-cells in an MHC-independent as well as -dependent manner (148,149). The majority of melanoma-infiltrating γδ T-cells shows an effector memory and terminally differentiated phenotype, and a higher rate of γδ T-cell infiltration, in particular of Vδ2 T-cells, correlates with early stage melanoma and absence of metastasis (150). Therefore, γδ T-cells are considered interesting candidates for adoptive T-cell therapy (151). Yet, the function of γδ T-cells should be carefully studied, as Vδ1 T-cells with immunosuppressive activity have been found in melanoma as well (152). In melanoma patients treated with CTLA-4 blocking antibodies, an increase in Vδ2 versus Vδ1 T-cells was linked to good versus poor survival (153). NKT-cells are also studied in melanoma. As they recognize lipids restricted by a non-classical class I-like molecule CD1d, they are also considered unconventional T-cells (154). The majority of NKT-cells in mouse and human are invariant NKT-cells that recognize α-galactosyl ceramide (α-GalCer). A final understudied unconventional T-cell subset is represented by MAIT-cells. In metastatic melanoma-patients treated with anti-

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PD-1 therapy, an increase in $CD8^+$ T-cells and MAIT-cells was demonstrated specifically in responders. As patients with >1.7% of MAIT-cells among the peripheral $CD8^+$ T-cell population showed a better response to treatment, MAIT-cells may be considered a biomarker for melanoma patients responding to anti-PD-1 therapy (155,156) (**Table 2**).

Various approaches to harness the immune system in the fight against melanoma are under investigation, from immunization strategies, including DCs, peptide (157,158) and nucleic acids (159) vaccines and the use of oncolytic viruses, exemplified by T-VEC ((160) reviewed in (161)), to cytokine therapy ((162–164) reviewed in (165)), inhibition of co-inhibitory ((166) reviewed in (167,168)) and/or stimulation of co-stimulatory (169–172) immune checkpoints, and adoptive T-cell therapies including engineered T-cells (173,174). These approaches mainly focus on enhancing the number and activity of $CD4^+$ Th1 and $CD8^+$ T-cells, while some yet not all also reduce the activity of Tregs. Approaches that also harness NK-cells have shown promise in preclinical studies (175,176), be it with suboptimal results, leaving room for improvement (177,178).

Without a doubt, immune checkpoint inhibition (ICI) of the CD80/86-CTLA-4 as well as the PD-1-PD-L1 pathway, has delivered and holds promise for other immunotherapies to treat melanoma. Yet its effectivity is currently hampered by the installation of inherent and adaptive resistance mechanisms, that may vary considerably among patients ((179–182) (reviewed in (183)). Moreover, 33-50% of melanoma patients treated with ICIs develop cutaneous immune-related adverse events (iRAEs) that can unfold as local or widespread rashes that can present as eczema, psoriasis, depigmentation and other skin disease variants, indicating the role of T-cell subsets in these conditions ((184–187) reviewed in (188)). Notably, a positive correlation between melanoma-associated leukoderma (depigmentation) and survival after immunotherapy has been described (reviewed in (189)).

3.8 Virus-induced skin cancers

Various oncogenic viruses have been identified, of which several are involved in skin cancer. The most prevalent cancer-associated virus is human papillomavirus (HPV), with HPV16 and 18 being the most important strains, causing cervix carcinoma, but also penile, vaginal, anal, and oro-pharyngeal cancer.

Head and neck squamous cell carcinoma (HNSCC) can be divided in HPV^+ and HPV^- tumors. Overall prognosis of HNSCC is worse than for SCC at other sites of the skin, but HPV^+ HNSCC shows a better prognosis than HPV^-

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cancers. Moreover, HPV^+ HNSCC respond better to ICIs, which might be attributed to their high-level infiltration of $PD\text{-}1^+$ T-cells, as PD-L1 status on the tumors was not different (190). Both for HPV^+ and HPV^- HNSCC, Treg infiltration is an independent prognostic factor (191). An interesting question that remains to be answered is whether HPV vaccines also protect against HPV^+ HNSCC.

Merkel cell carcinoma (MCC) is a rare but aggressive tumor of neuro-endocrine origin. They derive their name from the Merkel cells that can be found in the basal layer of the epidermis and play a role in touch sensation. The underlying cause of MCC is infection with an oncogenic polyomavirus (192). Oncoprotein-specific tumor-infiltrating $CD8^+$ T-cells were prevalent in MCC patients (193). ICI therapy has proven effective in the treatment of MCC, although about 50% of patients remain refractory (194) (**Table 2**). Presence of high numbers of T_{CM} with high TCR diversity was shown to be predictive of good response to ICI therapy (195).

Kaposi's sarcoma (KS) is a vascular tumor caused by human herpes virus type-8 (HHV-8) and is especially associated with late-stage HIV infections. Although $CD8^+$ T-cell infiltrates were observed in KS lesions, they were not associated with sites of HHV-8 infection (196). Stage-related PD-L1 expression was observed on KS tumors, suggesting that these types of tumors might benefit from ICI therapy (197).

4 Concluding remarks

The role of T-cells in inflammatory skin disorders is based on a complex interaction with innate immune cells, B-cells, and other cells in their microenvironment. The various T-cell subsets and their mediators affect activation, migration, differentiation, and function of local tissue and immune cells. This results in a critical involvement of T-cells in skin homeostasis and pathology. Development of effective T-cell (mediators) targeted biologicals for treatment of inflammatory skin diseases progressed rapidly during recent years, confirming the crucial role of T-cells and their mediators in inflammatory skin disorders. *Vice versa*, the response to the treatment, or their adverse events, can teach us about the underlying mechanisms and contribute to disease endotyping. Hence, ongoing and improved interdisciplinary research into the role of T-cell subsets in the skin is warranted to further increase our understanding of T-cell functions to pave the way towards novel and effective therapies to harness T-cells in inflammatory skin conditions.

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IX Tables:

Table 1: Characteristics of innate and adaptive subsets of T-cells and their function.

CCR: CC chemokine receptor; CXCR: CXC chemokine receptor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN-γ: interferon gamma; ILC: innate lymphoid cell; IPEX: Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; Lti: lymphoid tissue inducer cell; NK: natural killer; Tc: cytotoxic T-cell; Tfh: follicular T helper cells; Th: T helper; TNF-α: tumor necrosis factor alpha; Treg: regulatory T-cell.

Table 2: Available and promising therapeutic approaches to harness T-cells in skin disease.

CTLA-4: cytotoxic T lymphocyte antigen-4; IFN-α: interferon alpha; ILC: innate lymphoid cells; JAK: Janus kinase; NK: natural killer; PD-1: programmed cell death-1; PD-L1: ligand of programmed cell death-1; Th: T helper cell; TNF-α: tumor necrosis factor alpha; Treg: regulatory T-cell.

X Figure legends:

Figure 1: Schematic overview of the conventional and unconventional T-cell subsets.

During the maturation and selection process of T-cells in the thymus, surface markers are differently expressed. Naive T-cells further differentiate to their mature state depending on local cytokines.

Figure 2: Schematic overview of the functional properties of T-cell subsets under homeostatic condition and inflammatory skin diseases.

A. In healthy skin, both innate and adaptive immune cells are present in low numbers in the dermis. Cutaneous lymphocyte-associated antigen (CLA) is expressed on antigen-specific tissue residing memory T-cells (T_{RM}) or effector memory T-cells (T_{EM}). T_{EM} cells can recirculate to the peripheral blood. $CD4^+$ tissue resident regulatory T-cells are important to maintain the peripheral tolerance. **B.** Type I hypersensitivity is characterized by an IgE-mediated allergic inflammation and T helper (Th)2 polarization. An impaired

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epidermal barrier function leads to increased access for allergens, which are picked up by antigen-presenting cells (Langerhans cells or dendritic cells) in the epidermis. T-cells that are presented to these antigens express CLA and activate plasma cells to produce IgE in presence of IL-4. Sensitized mast cells respond adequately upon exposure to the allergens resulting in degranulation and release of various mediators, such as histamine, which can contribute to itch and inflammation. Th2-cells and type 2 innate lymphoid cells (ILC) are major sources of IL-5 and IL-13. **C.** Atopic dermatitis is a T-cell-mediated chronic relapsing inflammation of the skin. Th2-cells are the most abundant cells and responsible for the production of the pro-inflammatory cytokines IL-4, IL-5 and IL-13 together with ILC2s. Th2-cells produce IL-31 resulting in itch, which is a hallmark of atopic dermatitis. Also, Th1 and Th22-cells are present, which release interferon (IFN)-γ and IL-22, respectively. **D.** Psoriasis, γδ T-cells, dendritic cells and macrophages affect the Th17 and Tc17 cells, which are the dominating cells, but also Th1 and ILC3s are present. Release of IL-17A, IL-22 and tumor necrosis factor (TNF)-α results in erythematous scaly papules and plaques. **E.** In melanoma, T-cell infiltration is associated with prolonged survival and reduced risk of metastasis. $CD4^+$ Th1v-cells can recognize tumor-associated antigens (TAAs) and kill melanoma cells via production of IFN-γ, perforin and granzyme B. Via the CCL2/CCR2-pathway, unconventional γδ T-cells can recognize tumor-specific ligands. Presence of γδ2 is correlated to good prognosis compared to the presence of γδ1 T-cells, which is linked to bad prognosis. Responders to anti-PD-1 therapy increase $CD8^+$ T-cells and mucosal associated invariant (MAIT) T-cells.

CLA: cutaneous lymphocyte-associated antigen; CTLA4: cytotoxic T-lymphocyte associated antigen 4; IFN-γ: interferon-gamma; ILC: innate lymphoid cell; iNKT: invariant natural killer T; LT4: leukotriene 4; MAIT: mucosal associated invariant T; MHC: major histocompatibility complex; PGD2: Prostaglandin D2; TAA: tumor-associate antigen; Th: T helper; Treg: regulatory T-cell; T_{RM}: tissue-residing memory T; TSLP: thymic stromal lymphopoietin.

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Transcription factors	Tbet, STAT4	GATA3, STAT5	PU.1 IRF4	RORγt, STAT3	AHR BNC2 FOXO4	FoxP3	Bcl-6, C-Maf (BLIMP-1)
$CD4^+CD8^-$ Effector T cells	Th1	Th2	Th9	Th17	Th22	Treg	Tfh
$CD4^-CD8^+$ Cytotoxic T cells	Tc1	Tc2	Tc9	Tc17	Tc22	Treg	Tfh
Innate lineage equivalents	ILC1/NK cells	ILC2		Lti	ILC3		
Cytokines	IFN-γ, TNF-α, IL-2, GM-CSF, IL-18	IL-4, IL-5, IL-13, IL-31	IL-9	IL-17A/F, IL-6, IL-21, IL-22, GM-CSF, TGFβ, IL-12	IL-22, TNF-α	IL-10, TGF-β	IL-4, IL-21
Chemokine receptors	CXCR3, CCR5, CCR7	CCR3, CCR4, CCR8	CCR3, CCR6, CXCR3	CCR2, CCR4, CCR6	CCR4, CCR6, CCR10		Tfh1: CXCR5, CXCR3+, CCR6- Tfh2: CXCR5, CXCR3-, CCR6- Tfh17: CXCR5, CXCR3-, CCR6+
Function	Homeostasis, control of inflammation, anti-tumor responses	Recruitment of specialized subsets of immune cells	Immunity against helminths and tumors	Tissue repair	Tissue repair, keratinocyte proliferation, Innate immune response	Immunoregulatory, suppress Th1, Th2, Th17	Germinal center, promotes B cell maturation and function
Pathophysiology	Inflammation	Class switch of B cells, (allergic) inflammation, mucus production, remodelling, epidermal injury	Inflammation	Inflammation	Epithelial hyperplasia	IPEX	
Diseases	Intracellular bacteria and viruses	Atopic dermatitis, atopic diseases, helminth infections	Allergic inflammation, autoimmunity, cancer, helminths	Psoriasis, Autoimmunity, extracellular bacteria	Skin infections, atopic dermatitis, psoriasis, autoimmunity, cancer	Immune tolerance	Autoimmunity

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Table 2: Available and promising therapeutic approaches to harness T-cells in skin disease.

Target	T cell subset	Treatment	Status	Dermatologic conditions	References
IL-4/IL-13	Produced by Th2	Dupilumab	Approved	Atopic dermatitis	60, 61, 62
IL-13	Produced by Th2	Lebrikizumab, Tralokinumab	Phase III (ongoing) Phase III	Atopic dermatitis	63, 64, 65
IL-5 receptor	Produced by Th2	Benralizumab	Phase III (ongoing)	Atopic dermatitis, CSU	Clinicaltrials.gov
IL-17A	Produced by Th17	Ixekizumab, Secukinumab	Approved	Psoriasis, atopic dermatitis	80, 82 72, 81
IL-17R	Th17	Brodalumab	Approved	Psoriasis	83
p40 subunit of IL-12 and IL-23	Anti-IL-12p40	Ustekinumab	Approved	Psoriasis	83, 89, 90
p19 subunit of IL-23	IL-23 is important for Th17 maintenance and expansion	Tildrakizumab, Guselkumab, Risankizumab	Approved Approved Approved	Psoriasis	87 88 89, 90
IL-31 receptor A	Th2	Nemolizumab	Phase III	Atopic dermatitis, autoimmune skin diseases	71
TNF-α-receptor	Expressed by leukocytes	Etanercept	Approved	Psoriasis, psoriatic arthritis	84
TNF-α	Produced by and effect on CD4+ and CD8+ T cells, Tregs	Adalimumab, Infliximab, Certolizumab-pegol, Golimumab	Approved	Psoriasis, psoriatic arthritis, autoimmune disease, cancer	84
Janus kinase (JAK1, JAK2, JAK3)	Tyrosine kinases for phosphorylation and activation of receptors for T cell cytokines	Tofacitinib Ruxolitinib (topical) Abrocitinib (oral) Baricitinib (oral) Upadacitinib (oral)	Phase III Phase III Phase III Approved Phase III	Lichen planus, alopecia areata, dermatomyositis Vitiligo, alopecia areata Atopic dermatitis Atopic dermatitis Atopic dermatitis	113, 114 122 109 126 66, 68 67, 70 69

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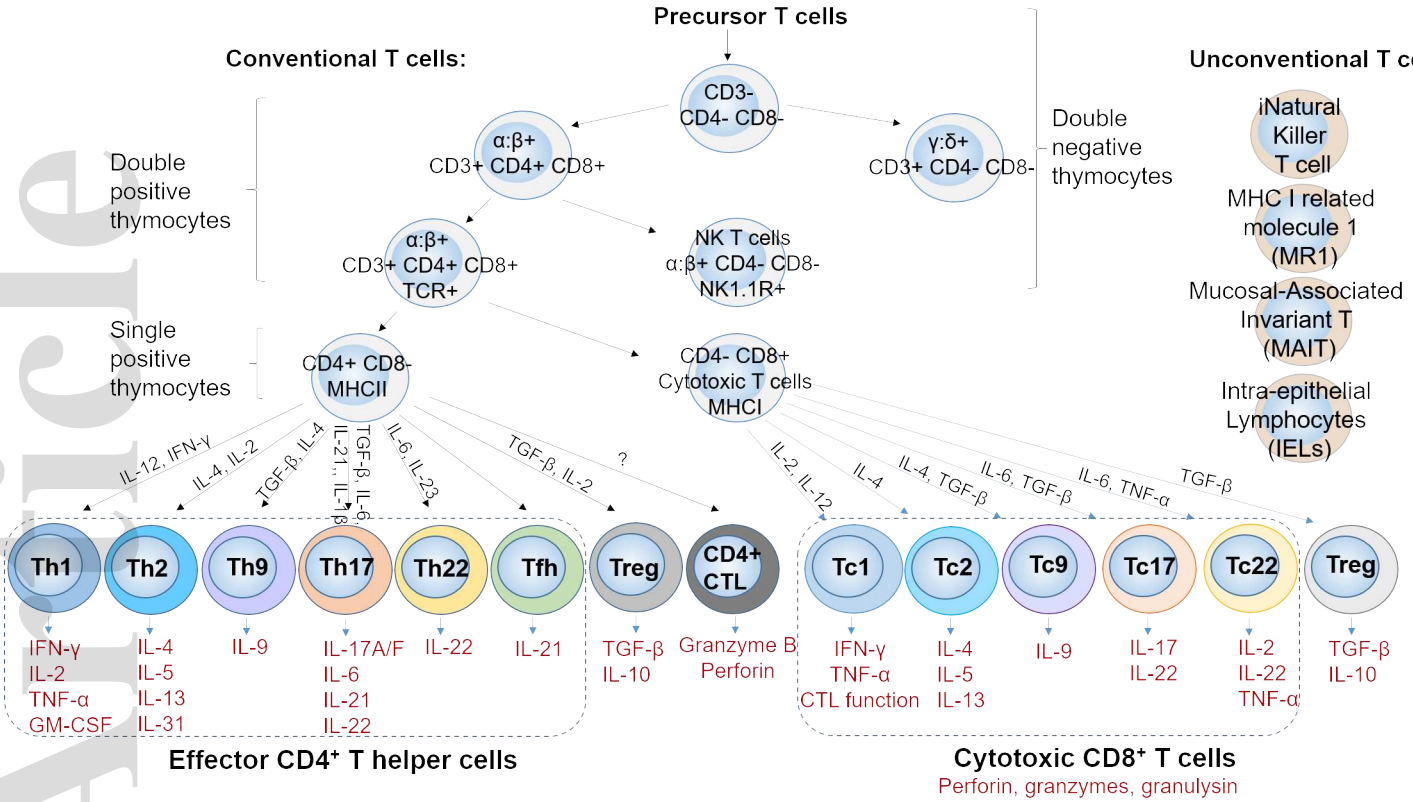
		Nintedanib	Approved	Systemic sclerosis	108
Programmed cell death-1 (PD-1)	Immune checkpoint proteins on T cells	Pembrolizumab, Nivolumab, Cemiplimab Tralokinumab	Approved	Melanoma (as monotherapy or in combination with ipilimumab) Basal cell carcinoma, Cutaneous squamous cell carcinoma and Merkel Cell Carinoma	161, 162, 191, 192, 193, 200
Programmed cell death ligand 1 (PD-L1)	Immune checkpoint proteins on T cells	Avelumab,	Approved	Melanoma, Merkel cell carcinoma	172, 174
cytotoxic T lymphocyte antigen-4 (CTLA-4)	Immune checkpoint proteins on T cells	Ipilimumab	Approved	Melanoma	159, 173, 174, 189, 190
Tumor cells	Expansion of antigen-specific T cells and tumor infiltration	Oncolytic virus vaccin (Talimogene Laherparepvec)	Approved	Melanoma	166, 167

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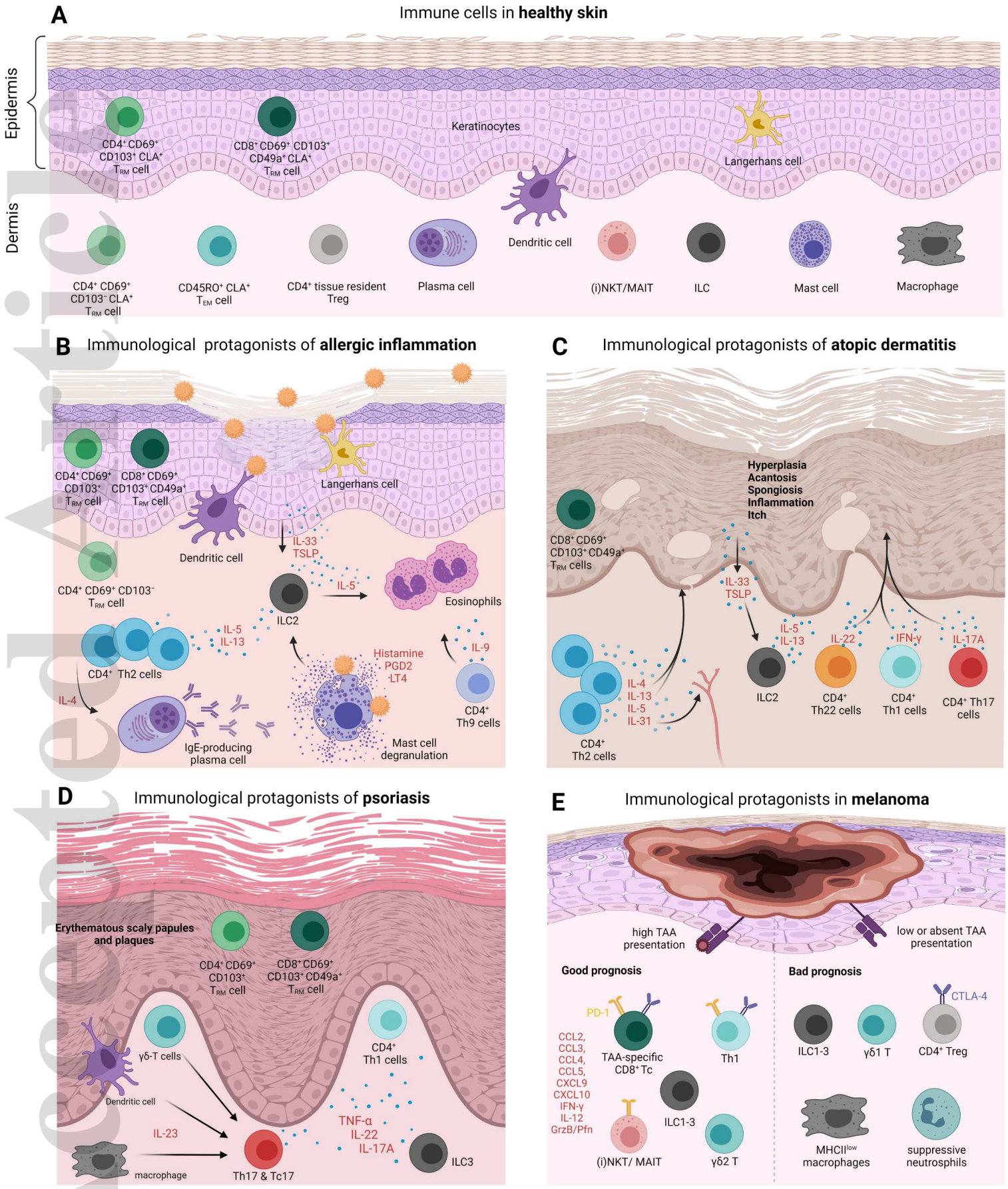
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