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REVIEW

Immunology WILEY

The attentive focus on T cell-mediated autoimmune pathogenesis of psoriasis, lichen planus and vitiligo

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Abstract

T cell-mediated autoimmune skin diseases develop as a result of the aberrant immune response to the skin cells with T cells playing a central role. These chronic inflammatory skin diseases encompass various types including psoriasis, lichen planus and vitiligo. These diseases show similarities in their immune-pathophysiology. In the last decade, immunomodulating agents have been very successful in the management of these diseases thanks to a better understanding of the pathophysiology. In this review, we will discuss the immunopathogenic mechanisms and highlight the role of T lymphocytes in psoriasis, lichen planus and vitiligo. This study could provide new insights into a better understanding of targeted therapeutic pathways and biological therapies.

1 | INTRODUCTION

Skin, the first barrier of defence, protects the body against external threatening elements.[1] Damage to and defect in this organ may result in colonization of the infectious pathogens or induction of inflammation.[2] Therefore, maintaining skin integrity is considered as a critical factor. Inflammatory skin diseases are among the common medical disorders with a high impact on patient quality of life and are associated with high psychosocial impact. Among them, psoriasis, lichen planus and vitiligo are considered to be T cell-mediated diseases where we have gained increasing knowledge in the last years on the pathophysiology leading to breakthrough therapeutic

options.[3] In these diseases, the definitive reason for the breakdown of self-tolerance, induction of inflammation and the onset of the autoimmune response is not well understood. Generally, injuries such as viral infections, trauma, chemical damages or exposure to extensive sunlight lead to damage to keratinocytes resulting in the release of Damage-Associated Molecular Patterns (DAMPs), which are then identified by the cells of the innate immune response such as dendritic cells expressing Toll-like Receptors (TLRs).[4,5] This process initiates innate immune responses that involve the production of inflammatory cytokines such as Interleukin-1 beta (IL-1β), IL-6, IL-8, tumour necrosis factor-alpha (TNF-α) and type I and II Interferons (IFN).[6] The production of these

cytokines promotes the activation of local myeloid DCs and up-regulation of chemokines such as CXCL9 and CXCL10 that initiates migration of T cells to the inflamed lesions and enhances the T cell-mediated inflammation.[7,8] Although psoriasis, lichen planus and vitiligo diseases have differences regarding how they stimulate the immune system, they have very much the same immunopathogenesis processes. As if, Vajaitu C et al reported due to the homogeneous essence of psoriasis, lichen planus, and vitiligo, the coexistence of all three diseases can emerge in one person.[9]

Currently, topical corticosteroids, or anti-inflammatory drugs including, calcineurin inhibitors such as cyclosporine and tacrolimus, mycophenolate, azathioprine and methotrexate are used as non-specific treatment regimens for these diseases.[10-12] Among these, the immunotherapy, an excellent tool to combat immune perturbations, has been strongly considered as a specific medication in this field. A better perception of the common mechanisms of these diseases may be effective in finding a way to limit their complications. Firstly, we will introduce the immunopathogenesis mechanism of psoriasis, lichen planus and vitiligo diseases in brief and then will discuss the common adaptive immune cells and pathways in these diseases.

2 | THE IMMUNOLOGICAL PHENOMENON INVOLVED IN PSORIASIS

Psoriasis is another chronic autoimmune disorder that affects approximately 2%-4% of the world's population with a higher prevalence in northern countries.[13] The most common type of psoriasis is plaque psoriasis with the most prominent feature of sharply demarcated erythrosquamous plaques.[14] The hyperproliferation and abnormal differentiation of keratinocytes is the hallmark of psoriasis.[15] Beside skin psoriasis may also affect other organs such as joint causing psoriasis arthritis seen in up to 30% of psoriatic patients.[16]

The immune process activates as a consequence of the skin damage induced by environmental and internal factors (Table 1). Keratinocytes respond to these stimuli through TLRs, Nod-Like receptors (NLRs) and inflammasome which lead to the production of pro-inflammatory cytokines.[17] Secretion of biological substances including antimicrobial peptides (AMPs), cytokines and chemokines such as IL-1 family, IFN-I, TNF-α, IL-6, CXCL1, CXCL8, CXCL10 and CCL20 initiate the innate and adaptive immune activation.[18] Keratinocyte-derived AMPs bind to self-DNA as complex and are captured by plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) through TLR7 and TLR8.[19] Antigen processing and presentation to T lymphocytes in local lymph nodes results in T cell activation and Th1/Th17/Th22 differentiation.[20]

TNF-α, IL-17 and IL-22, the main operators of the Th1/Th17/Th22 pathway, lead to neutrophil and NK cell infiltration, hyperproliferation of keratinocytes, and epidermal thickening (Figure 1). The crosstalk between autoreactive T cells and skin-resident keratinocytes occurs following the auto-antigen recognition including the LL-37 cathelicidin/nucleic acid complexes and newly generated lipid antigens.[21] Self-DNA in complex with endogenous antimicrobial peptide (LL-37, cathelicidin) function as an auto-antigen and can activate pDCs through TLR9 involvement. This complex can also be exhibited by HLA-C*06:02 molecules and specifically stimulate T cells through the HLA-TCR complex. In addition, the melanocytic antigen ADAMTSL5 in complex with LL37 presented by HLA-C*06:02 can stimulate pathogenic CD8^{+} T cells.[22] Among the most important upstream signals is the IL-23 released by inflammatory and activated DCs skewing immune response into Th17; also being a very important pathway in the immunopathogenesis of psoriatic arthritis. Mice that had high levels of IL-23 in the skin (K23 mice, which are generated based on the previously described protocol) develop a psoriasis-like disease that is characterized by parakeratosis, hyperkeratosis, acanthosis and increased inflammatory conditions in the dermis.[23]

3 | INTERACTION OF IMMUNE CELLS WITH STROMAL CELLS IN PSORIASIS

The interaction of immune cells with cells and products of stromal tissue has a crucial role in causing inflammation in autoimmune diseases. In psoriasis, the interaction between epidermal and immune cells is common. To develop the establishment of new therapeutic strategies in this section, we discuss the interaction of skin stromal cells and immune cells. Given that the studies are very limited in this field for lichen planus and vitiligo diseases, in this section, we only focus on psoriasis.

3.1 | Skin stromal cells

3.1.1 | Skin fibroblasts

One of the most important components of the skin is dermal fibroblasts. They produce and organize the extracellular matrix (ECM) of the dermis as well as communicate with each other and other cell types, playing an essential role in the function of skin physiology.[24]

It has been shown that DCs interact with fibroblasts during immune responses and fibroblasts enhance IL-23 secretion from DCs treated with lipopolysaccharide.

TABLE 1 Environmental and internal triggers of psoriasis

External factors	Examples
Patient related	
Smoking	
Alcohol consumption	
Pregnancy	
Menstrual Cycle	
Diet	
Obesity	
Environmental	
Stress	
Temperature	Cold Weather, Low humidity
Sunlight	UV
Skin Injury (Trauma)	Cut, Scrape, Surgical wound, Tattoo, Burn/Sun-burn
Disease and treatment related	
Allergy	
Infections	Streptococci Throat
Medications	Beta Blockers, ACE inhibitors, Lithium, Hydroxychloroquine/ Chloroquine/ Quinacrine/ Plaquenil, Interferons, NSAIDs, Terbinafine, Tetracycline, TNF inhibitors
Internal factors (Genetics)	**SNP**
HLA Gene polymorphis	
HLA-B13	
HLA-B17	
HLA-B57	
HLA-Cw6	rs1265159, rs1265181, rs4406273, rs10484554
Non-HLA Gene polymorphism	
Interleukin 12 B	rs6887695
Interleukin 23 receptor	rs11209026
CARD14	rs144475004, rs387907240, rs281875215, rs587777763, rs281875214, rs281875212, rs281875213, rs281875214

Abbreviations: ACE, angiotensin converting-enzyme; CARD14, caspase recruitment domain family member 14; HLA, human leucocyte antigen; NSAID, nonsteroidal anti-inflammatory drugs; SNP, single nucleotide polymorphisms; TNF, tumour necrosis factor.

Activated DCs produce IL-1β/TNF-α, which stimulates prostaglandin E2 (PGE2) production by fibroblasts. PGE2 affects activated DCs that increase their IL-23 release. Fibroblast-stimulated DCs also play a crucial role in promoting the Th17 expansion in an IL-23, Cox-2 -dependent manner. In psoriasis, due to the important role of IL-23/ Th17, high expression of Cox-2 in fibroblasts was observed.[25] Recruited Th17 cells into the psoriatic inflammatory site interact with local mesenchymal cells such as skin fibroblasts. Noack et al showed that interactions between resting peripheral blood mononuclear cells (PBMC) and psoriatic skin fibroblasts induce IL-8, IL-6 and IL-1β production. Activation of blood-derived immune cell and fibroblast interactions are critical for a high IL-17 secretion.[26] These results showed that fibroblasts contribute to

promoting IL-23 release and expansion of Th17 cells that involved in psoriatic pathogenesis. Modulation of skin fibroblasts along with other treatment strategies can help the control of patients with psoriasis.

3.1.2 | Epidermal Stem Cells (ESCs)

Furthermore, epidermal stem cells (ESCs) are cells with a long lifespan and proliferative property that resides in the epidermal basal layer. The overexpansion of ESCs cells in psoriasis can due to the niche factors from the recruited immune cells, secretion of growth factors and inflammatory cytokines by immune cells. As mentioned above, the cytokines secreted by Th17 such as IL-17A, IL-22, have
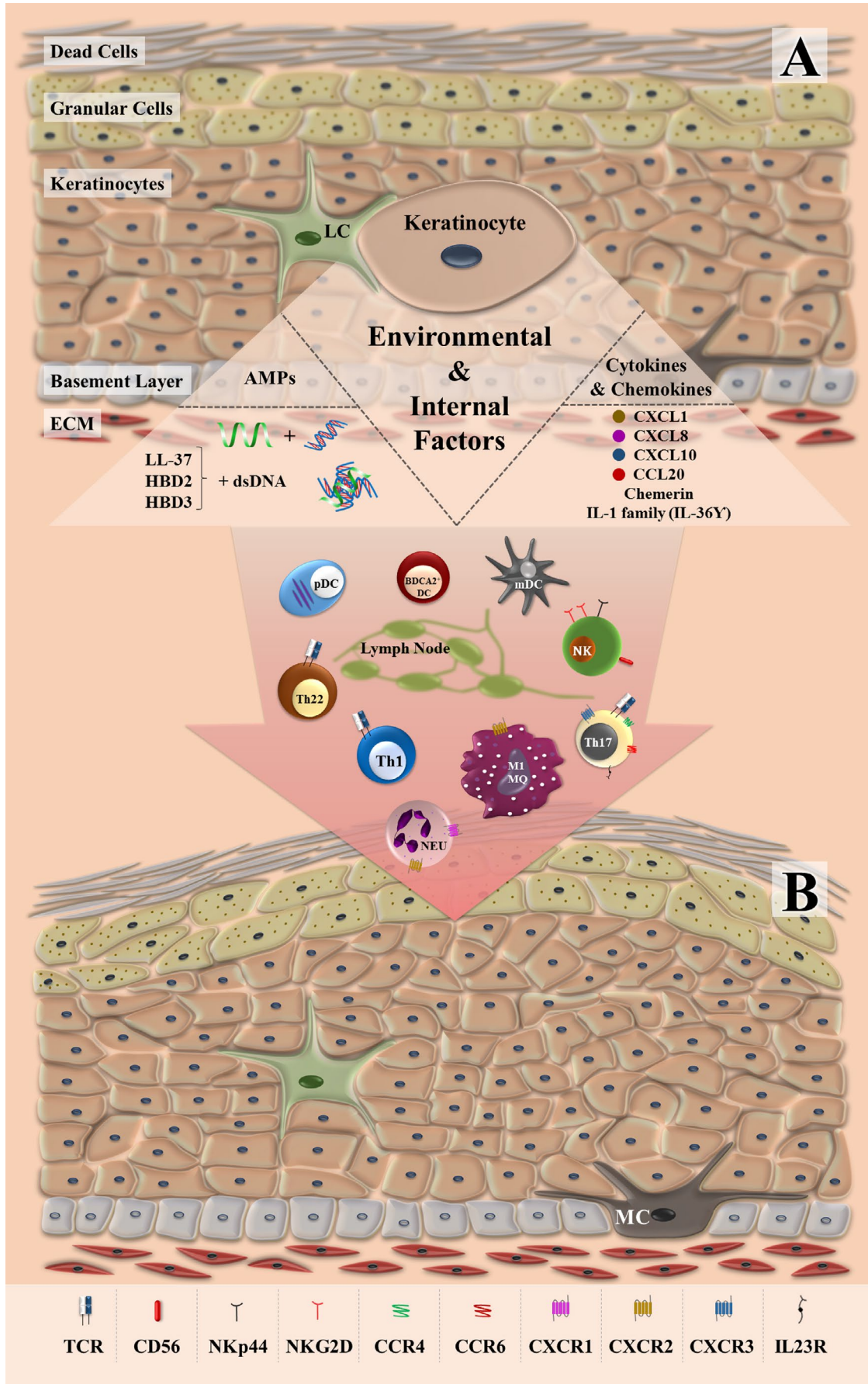
a central role in the pathogenesis of psoriasis. These cytokines can activate the ESCs from a silent state into an active and hyper proliferative state, whereas suppressing keratinocyte differentiation.[27,28]

3.1.3 | Dermal mesenchymal stem/stromal cells (MSCs)

Mesenchymal stem cells are multi-potential cells that may differentiate to chondrocytes, osteoblasts and adipocytes. These stem cells can easily be isolated from umbilical cord blood, bone marrow, dermis, liver and fat. The MSCs have immunomodulatory effects, including inhibition of dendritic cell maturation, suppression of activated T cell and natural killer cell proliferation, and regulation of inflammatory cytokine secretion. However, there are many ambiguities about the immunosuppressive function of the MSCs in patients with psoriasis.[29]

The dermal MSCs overexpress the VEGF and nitric oxide (NO) in patients with untreated psoriasis and promote the dermal capillaries proliferation. Produced VEGF in addition to the pro-angiogenic property, can also act as a chemotactic factor for recruiting plasmacytoid dendritic cells (pDCs) and lead to the inflammatory microenvironment in psoriatic lesions.[30] In addition, the psoriatic dermal MSCs co-cultured with activated T cells in vitro showed lower inhibition ability on the proliferation of T cells.[31]

In general, evidence indicates that activated T cells in psoriasis induce activation of ESCs and promote the immune-modulatory MSCs into a pro-inflammatory MSC phenotype, which involves in the angiogenesis and recruitment of immune cell to psoriatic dermal by secreting of chemokines as well as inflammatory cytokines, and finally exacerbation the local Th immune response.[32]

4 | IMMUNE MECHANISMS IMPLICATED IN LICHEN PLANUS

Lichen planus (LP) is a non-infectious autoinflammatory disease which affects skin, nails, oral and genital mucosal.[33] LP may involve various mucosal surfaces either independently or concurrently (oral, skin and oral and skin lesions). Oral form may precede or accompany the skin lesions or it may be the only manifestation of the disease.

The prevalence of skin LP in the general population is 0.9%-1.2% and the prevalence of oral LP is reported between 0.1% and 2.2%.[34] In a recent study by Omal PM et al from 18 306 patients screened, LP prevalence was (0.64%) with oral lichen planus (OLP) prevalence was (0.4%), skin lichen planus (SLP) was (0.06%) and OLP and SLP was (0.13%).[34] LP is a chronic, inflammatory, autoimmune disease that affects the skin, oral mucosa, genital mucosa, scalp and nails. LP lesions are described using the six P's (planar [flat-topped], purple, polygonal, pruritic, papules, plaques). Although the exact aetiology of lichen planus is unknown, an immune-mediated pathogenesis is recognized. A meta-analysis of primarily case-control studies conducted in multiple countries found a statistically significant association between hepatitis C virus (HCV) infection and lichen planus, although there is no known explanation for this association.[35]

There are different causes for this disease, however, T cells play a critical role in its pathogenesis and disease progression.[36] The accumulation of T cells in the dermal-epidermal or basal membrane, which is triggered by an uncontrolled cellular immune response to cell death in keratinocytes, is the hallmark of this inflammatory disorder (Figure 2). It has been suggested that specific memory T cells for previous virus exposure could cross-react with other antigens, including drugs, contact allergens and other different viruses in the absence of homogenous antigen, and lead to epidermal destruction. This theory could explain the link between exogenous factors such as viruses and drugs and the development of lichen planus.[37]

Antigen presentation and stimulation of the immune system through extrinsic and intrinsic mediators is the initial step of the immunopathogenesis of autoimmune disorders. Following the environmental triggers such as stress, smoking and drugs, the keratinocytes might get damaged and as a consequence release auto-antigens such as myeloid-related protein S100A8/A9.[38,39] These self-proteins will be recognized by TLRs on the surface of antigen-presenting cells (APCs) in lichen planus and lead to pro-inflammatory cytokine production such as IFN-γ.[40,41] In addition, following the local inflammation, intra- and extracellular antigens are processed by keratinocyte and presented through MHC-I and MHC-II- peptide complexes to CD8+ and CD4+ T lymphocyte, respectively. Cytotoxic T lymphocytes (CTLs) and T helper (Th) cells are activated via antigen recognition on the keratinocyte surface, which leads to cytokine production and T cell differentiation. Perforin/Granzyme and
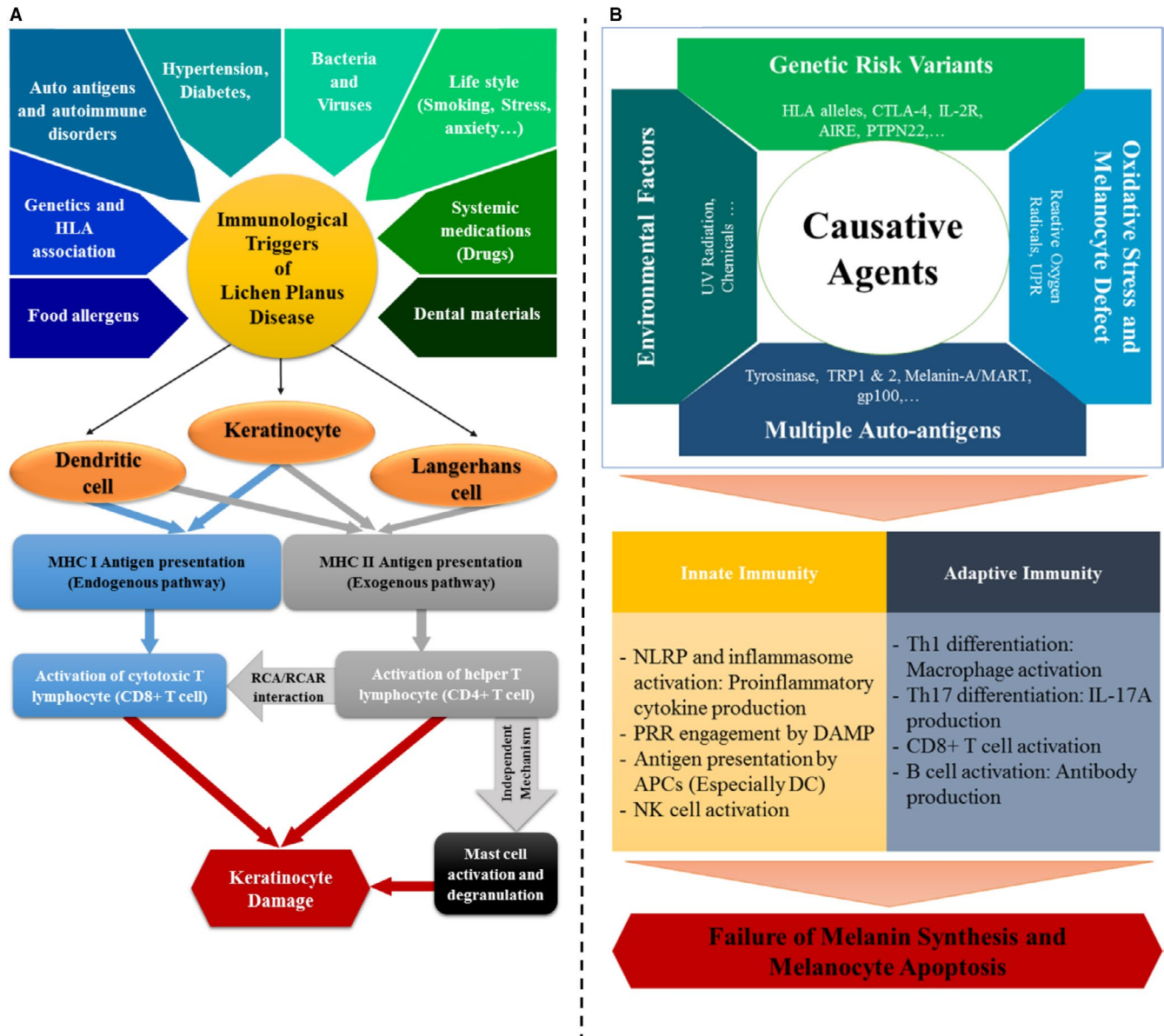
FIGURE 2 Diagram of the developmental process of innate and adaptive immune activation in lichen planus (A) and vitiligo (B) disease. In genetically susceptible individuals and environmental agents cause skin cell damage such as epithelial cells, keratinocytes and melanocytes. Damaged cell induces the inflammatory mechanisms including inflammasome activation, antigen presentation, T and B cell proliferation, subsequently. The local inflammation amplifies the further destruction of skin cells as a positive loop. APC, antigen-presenting cell; CTLA, cytotoxic T lymphocyte-associated protein; DAMP, damage-associated molecular patterns; DC, dendritic cell; HLA, human leucocyte antigen; IL, interleukin; MART, melanoma antigen recognized by T cells; MHC, major histocompatibility complex; NK, natural killer; NLRP, pyrin domains-containing protein; PRR, pattern recognition receptor; PTPN, protein tyrosine phosphatase non-receptor type; RCA, regulators of complement activation; Th, T helper; TRP, tyrosine related protein; UPR, unfold protein responses

pro-inflammatory cytokines including IFN-γ and TNF-α are released and induce apoptosis of keratinocytes and infiltration of Macrophages (MQs) and Natural Killer (NK) cells to the inflamed lesion. Dendritic cells (DCs) and Langerhans cells (LCs) are activated through inflammatory cytokines and exacerbate adaptive immune response, which is leads to keratinocyte damage forming a vicious cycle.[39] The interaction of Regulators of Complement and RCA receptor, which expressed on CD8^{+} and CD4^{+} T lymphocyte, respectively, results in CTL activation, keratinocyte apoptosis and epidermal damage.[42]

Aside from adaptive immune cells, Mast Cells (MCs) are pervaded through RANTES chemokine, which is released by activated T cells. MC activation and degranulation occurs as an independent non-specific pathway that yields to collagen cleavage and basal layer interruption[43] (Figure 3).
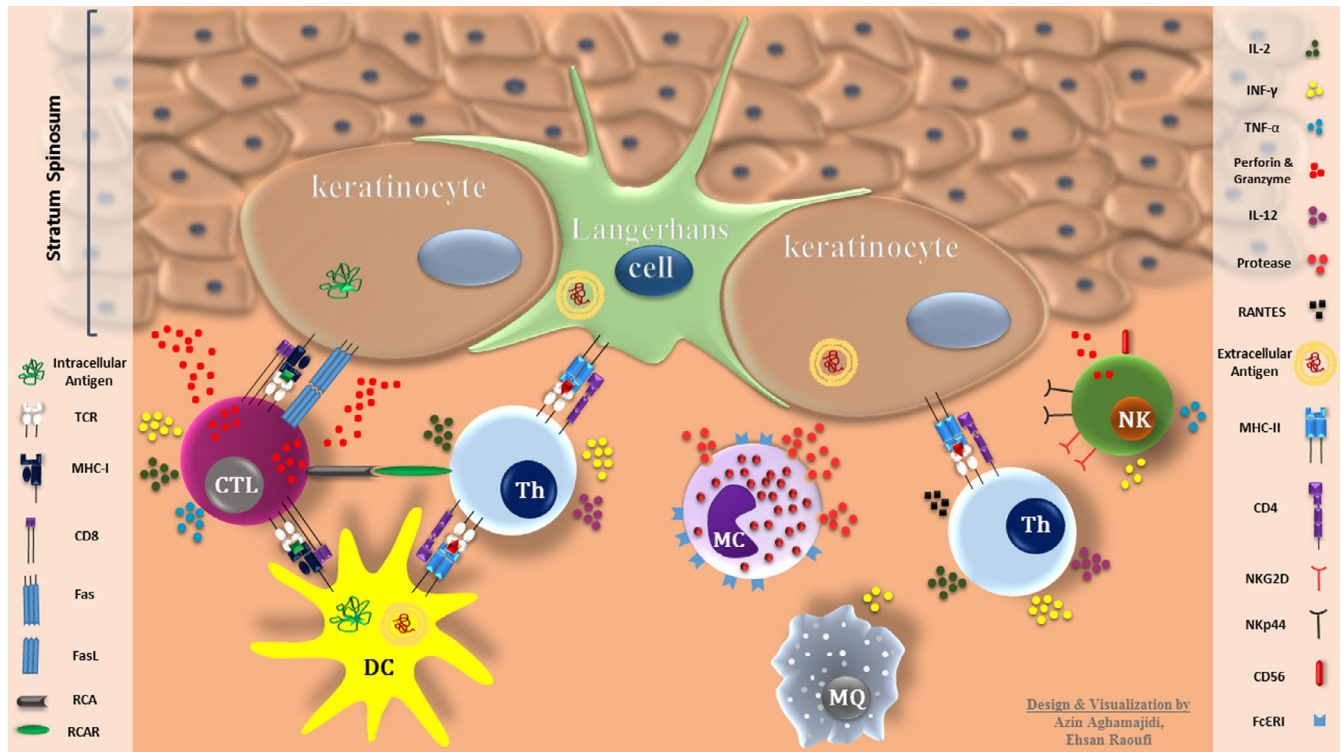
FIGURE 3 Immunopathogenesis mechanism of Lichen Planus disease. The immunological process of lichen planus disease was initiated by self or non-self-peptides presentation with keratinocytes to CD8 + and CD4 + T lymphocytes which migrate to the epidermal layer following the chemokine secretion. CD8 + T lymphocytes (CTLs) were activated by MHC-I-peptide complex expressed on keratinocyte surface or through activated CD4 + T lymphocyte (Th) by RCA-RCAR interaction. CTLs induce apoptosis in keratinocytes which are mediated by perforin-granzyme secretion, TNF-α production or Fas-FasL interaction. Likewise, Langerhans cells and DCs were activated by inflammatory cytokines and aggravate antigen presentation to T lymphocytes. CTL, cytotoxic T cell; DCs, dendritic cells; FasL, Fas ligand; FCεRI, fragment crystallizable ε receptor I; IFN, interferon; IL, interleukin; MC, mast cell; MHC, major histocompatibility complex; MQ, macrophage; NK, natural killer; RATES, regulated upon Activation, normal T cell expressed and secreted; RCA, regulators of complement activation; RCAR, RCA receptor; TCR, T cell receptor; TNF, tumour necrosis factor

5 | IMMUNOPATHOGENESIS OF VITILIGO

Vitiligo, an acquired pigmentary disorder of unknown origin, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1%. The disorder can be psychologically devastating and stigmatizing, especially in dark-skinned individuals. Vitiligo is clinically characterized by the development of white macules due to the loss of functioning melanocytes in the skin or hair, or both.[44] The immunopathogenesis of vitiligo is not well understood. Diverse types of immune cells including Innate Lymphoid Cells (ILC), Dendritic Epidermal T cells (DETC) and MQs are present in the epidermis layer of normal skin.[1] Environmental factors including UV radiation, chemical agents like phenol, monobenzone and other used in commercial products such as hair dyes constantly affect the surface of the skin.[45,46] These agents are sensed by tissue-resident cells which can induce the Endoplasmic Reticulum (ER) stress and Unfold Protein Responses (UPR), especially in melanocytes.[47]

Following the UPR, DAMPs are released through melanocytes that stimulate immune responses in susceptible individuals (Figure 2). Several loci containing MHC and non-MHC genes implicate in vitiligo development (Table 2) explaining the genetic background of the disease. The immune system can be activated through inflammasome activation and pro-inflammatory cytokine production, such as IL-1β, IL-6 and IL-8.[48] DCs activated via pro-inflammatory cytokines display auto-antigens of melanocytes to CD4+ T lymphocytes.[49] Following different cytokine production, CD4+ T cells differentiate into Th1/Th17 lymphocytes.[50] Th17, which is induced by IL-23 and IL-6, is a key player of vitiligo progression through IL-17, IL-21 and IL-22 production. IL-17, the main immunological feature of the vitiligo, affect the melanocyte damage through different routes.[51,52] Morphological alteration of melanocyte through IL-17, reduction of Melanocyte Inducing Transcription Factor (MITF, and its downstream genes as well as the decline of anti-apoptotic molecules such as BCL2 lead to melanin depletion. On the other hand, IL-17 orchestrates the induction of IL-1β, IL-6 and TNF-α by

TABLE 2 SNPs associated with vitiligo

GenBank ref.seq/Accession number	Gene name
The Major Histocompatibility Complex (MHC) locus	
rs12206499	HLA-A*02 MHC
rs3823355	Class I allele
rs532098	HLA-DRB1 gene
rs3823355	HLA-A gene
Other locus	
rs1464510	LPP
rs8192917	GZMB
rs11203203	UBASH3A
rs229527	C1QTNF6
rs2476601	PTPN22
rs231775	CTLA4
rs2670660	NLRP1
rs6502867	
rs2269577	XBP1
rs13208776	SMOC2
rs1393350	TYR
rs4908760	RERE
rs13076312	LRP
rs706779	IL2RA

Note: Vitiligo emerges to cause by a complex combination of autoimmune, genetic and environmental factors. Many SNPs in genes involved with immune system function are associated with vitiligo are.

Abbreviations: C1QTNF6, C1q and tumour necrosis factor related protein 6; CTLA-4, cytotoxic T lymphocyte-associated protein 4; GZMB, granzyme B; HLA, human leucocyte antigen; IL, interleukin; LPP, lipoma-preferred partner; LRP, leucine-responsive regulatory protein; NLRP, Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing; PTPN22, protein tyrosine phosphatase non-receptor type 22; RERE, arginine-glutamic acid dipeptide repeats; SMOC, SPARC related modular calcium binding; TYR, tyrosinase; UBASH3A, ubiquitin associated and SH3 domain containing A; XBP, X-box binding protein.

keratinocytes and fibroblasts which can activate the MQs and NK cells. Infiltration of these inflammatory cells to the skin leads to melanocyte damage and pigment loss.[51]

Identification of auto-antigens to optimize the diagnostic and prognostic methods as well as therapeutic tools is important in vitiligo. There are specific cytotoxic T lymphocyte responses against MelanA (MART1) in patients with vitiligo. Specific auto-antibody responses to Melanin-Concentrating Hormone Receptor 1 (MCHR1) auto-antigen appear to have the capacity to prevent the binding of the melanin-concentrating hormone to its receptor, but their main role in the pathogenesis of vitiligo is still unclear.[53] Following activation of CD4^{+} T cell and TNF-α production, B lymphocytes undergo differentiation, clonal expansion and finally anti-melanocyte antibody production. Different types of auto-antigens can stimulate antibody production, including tyrosinase, tyrosine hydroxylase, Tyrosine Related Protein 1 & 2 (TRP1/gp75 & TRP2), Melanin-Concentrating Hormone Receptor 1 (MCHR1), Pmel17, transcription factor SOX10 and pigment cell surface antigen.[54-61] Hypothetically, melanocyte activity and melanin production are then inhibited by auto-antibodies and Antibody-Dependent Cell Cytotoxicity (ADCC) process.[62,63] However, DCs or skin-resident LCs represent auto-antigens to CD8^{+} T cells and results in CTL activation.[64] Melanocyte destruction occurs through Perforin/Granzyme B, TNF-α production or Fas/FasL interaction.[65,66] Nevertheless, further researches are needed to explain the exact mechanism of the immunopathogenesis of vitiligo (Figure 4).

6 | COMMON T CELL LINEAGES IN THE PATHOGENESIS OF PSORIASIS, LICHEN PLANUS AND VITILIGO

In the following, we investigate how various cellular-mediated immune responses evolve in above mentioned inflammatory skin diseases. In addition, T cell heterogeneity, plasticity and the mixed infiltrate found in psoriasis, lichen planus and vitiligo which address the complexity of skin immunopathology was shown in Figure 5.

6.1 | T helper 1 (Th1)

Th1, a subset of CD4^{+} T lymphocytes, are among the most influential cells in adaptive cellular immune responses. Th1 cells differentiate through IL-12 and IFN-γ cytokines produced by innate immune cells such as DCs and NK cells. These cytokines lead to activation of T-bet as the key transcription factor of Th1 cells.[67] IFN-γ, TNF-α and IL-2 are the main immune response initiators produced by Th1. IFN-γ production is the hallmark of psoriasis, lichen planus and vitiligo, leading to inflammatory responses and tissue damages.[68-70] IFN-γ raises the sensitivity of epithelial cells, keratinocytes and CTL activation through the up-regulation of MHC class I. It also increases the expression of MHC class II on DCs and MQs, which enhances the antigen presentation to CD4^{+} T cells. TNF-α, another cytokine of Th1, has a synergistic effect with IFN-γ on the destruction of keratinocytes and melanocytes.[71] Furthermore, IL-2 produced by Th1 plays a role in the progression of keratinocyte and melanocyte apoptosis by increasing the activity of CD8^{+} T cells. This cytokine also has a positive feedback loop on Th1 proliferation. Javvadi LR, et al showed the contribution of Th1 activity in damage of endothelial cells, epithelial cells and keratinocyte in lichen planus.[72]
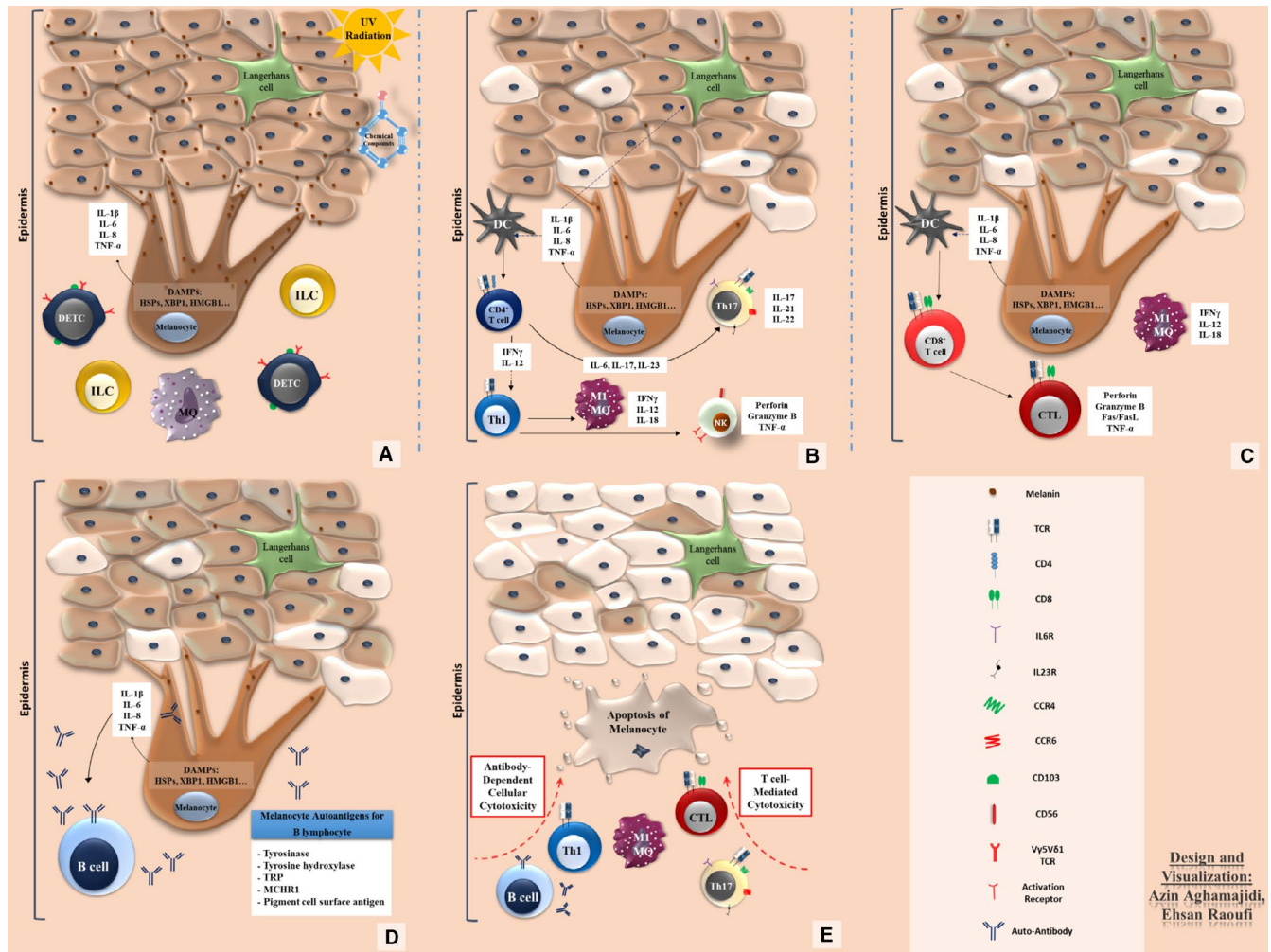
FIGURE 4 Immunopathogenesis mechanism of vitiligo. A, Immune cells involved in the normal epidermis of the skin. Various types of immune cells including LCs, DETC, MQs, ILCs and, etc are present in the skin as the first line of defence against invading and environmental agents. B, CD4^{+} T cell-mediated immune activation in the pathogenesis of vitiligo. The immunopathogenesis of vitiligo initiates through cellular stress response of melanocytes and helper T cell activation that results in T helper differentiation and inflammatory cytokine secretion. C, CD8^{+} T lymphocyte-mediated cytotoxicity of the melanocyte. Activation of CD8^{+} T lymphocyte (CTL) results in melanocyte destruction and focal depigmentation. D, B cell differentiation and antibody production in the immunopathology of vitiligo. Diverse types of auto-antibodies may attack the melanocytes and lead to further depigmentation of the skin. E, Procession of immune contributors to melanocyte apoptosis. CTL, cytotoxic T lymphocytes; DAMP, damage-associated molecular patterns; DC, dendritic Cell; HSP, heat shock proteins; IL, interleukin; ILC, innate lymphoid cell; IFN, interferon; MQ, Macrophage; TNF, tumour necrosis factor; DETC, Dendritic Epidermal T cell; XBP, X-box binding protein

6.2 | T helper 9 (Th9) and inflammation mechanism

Th9 cells, new subsets of CD4^{+} T lymphocytes, have been recently studied in psoriasis, lichen planus and vitiligo. These cells have been found to be the major resident T cells of the skin in normal individuals and appear to function in defence against certain pathogens.[73,74] Previous studies have reported the role of the Th9 cells in a variety of autoimmunity, especially in causing inflammatory conditions.[75,76] Th9 cell plays a significant role in causing inflammation in psoriasis, lichen planus and vitiligo diseases and exacerbates the function of other inflammatory cells such as Th1 and Th17.[77-80] There is also a direct relationship between the number of

Th9, the severity of the disease, and the period of inflammation.[81,82] In addition, it has been shown that Th2 cells are able to switch to Th9 under the influence of TGF-β and IL-4.[83] IL-9 is the major Th9 inflammatory cytokine, which has different effects on inflammatory conditions through Th17 proliferation.[79] It also affects the APCs in the skin and enhances IL-1β and IL-6 cytokine production. Studies have shown the direct relationship between IL-9 and the release of Matrix Metalloproteinase 9 (MMP9). MMP9 involves in the destruction of the Extracellular Matrix (ECM), the basal membrane and eventually, the apoptosis of keratinocytes and epithelial cells.[79] It has also been shown that the IL-9 blockade reduces MMP9 production by neutrophils.[84] The results of IL-9 inhibition indicate that IL-9 is essential for
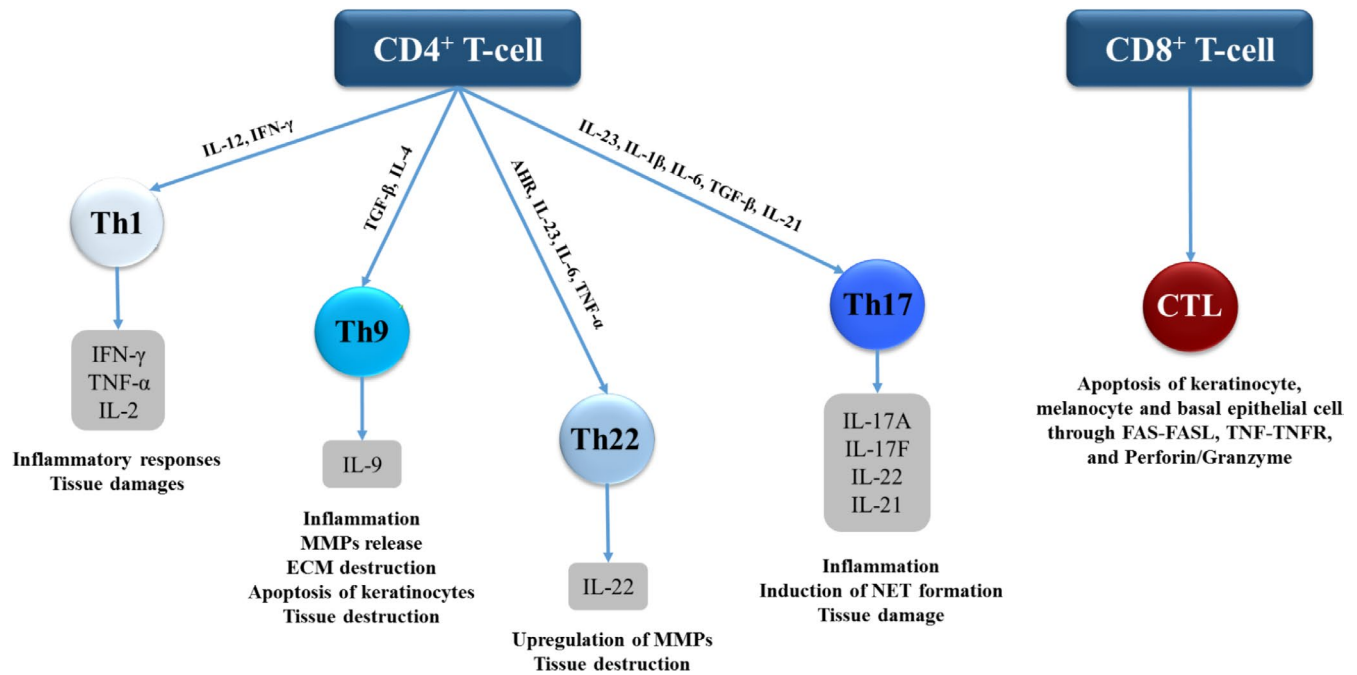
FIGURE 5 The static view of T cell subpopulation involved in the immunopathogenesis of psoriasis, lichen planus and vitiligo. Helper and cytotoxic T cells are the main contributor to the skin inflammation in psoriasis, lichen planus and vitiligo. Activation of helper T cells leads to Th1, Th9, Th17 and Th22 differentiation which is damage the epithelium layer and induce the ECM destruction by inflammatory cytokine production, MMP secretion and NET formation. CTLs induce apoptosis in keratinocytes, melanocyte and basal epithelial cells through FAS-FASL, TNF-TNFR and Perforin/Granzyme pathways

IL-17, IL-13 and IFN-γ production.[74] In addition, blocking of IL-9 in mice prevents blood vessel formation and Vascular Endothelial Growth Factor (VEGF) production.[85] Evidently, IL-9, which acts on MC, may play a crucial role in release of VEGF and inflammation, especially in psoriasis.

6.3 | Th17 and IL17/ IL23 pathways

Recently, the IL-23/IL-17 axis is considered fundamental in the pathogenesis of psoriasis, lichen planus and vitiligo. IL-23 and IL-17-secreting Th17 cells are key players to promote the inflammatory process in these diseases. Th17 is a subset of CD4+ T cells that contain Retinoic Acid receptor-related Orphan Receptor-γt (RORγt) and IRF4 transcription factors and identified by predominantly IL-17 cytokine production.[86] It has been shown that in psoriasis, lichen planus and vitiligo, the number of Th17 and IL-17 compared to the healthy persons increased, indicating enhancement of inflammatory conditions in the pathogenesis of these diseases.[87-89] Following the skin damage, CD4+ T cells were differentiated into Th17 through mDCs cytokine signalling including IL-23, IL-1β, IL-6, TGF-β and IL-21.[90] Th17- secreted IL-17, IL-22 and TNF-α can stimulate the production of TNF-α, IL-1β and IL-6 by keratinocytes, melanocytes, fibroblasts, MQs and DCs.[91] IL-17 is the main cytokine of Th17 that plays a critical role in the pathogenesis of autoinflammatory

diseases and exacerbation of inflammation. IL-17 enhances the production of Intercellular Adhesion Molecule 1 (ICAM-1), CCL20, CXCL1, CXCL3, CXCL5, CXCL6, CXCL8 which accumulate and recruit DCs, memory T cells and neutrophils to the damaged lesions.[28,92] CXCL1 and CXCL8 attract and enhances neutrophil activity in the skin, causing tissue damage by forming the Neutrophil Extracellular Traps (NET).[93,94] Neutralization of IL-17 has a direct relationship with reducing neutrophil chemotaxis and the severity of the disease. Studies in vitiligo indicate that IL-17 may shrink the melanocytes, inhibit melanogenesis and induce autophagy by impairing mitochondria function through the enhancement of IL-1β, IL-6 and TNF-α.[95,96] IL-17 has been implicated in the induction of keratinocyte proliferation in psoriasis, causing inflammation and plaque formation. This cytokine also enhances IL-9 production, which is involved in the production of CXCL8, IL-20, IL-1β and MMP1.[97]

Simultaneously, the pivotal role of IL-23 has been determined in a variety of autoinflammatory diseases. IL-23 has a critical role in the differentiation and expansion of functional Th17 cell subset through the IL-23 receptor (IL-23R) signalling. The interplay of IL-23/IL-23R on Th17, activates the Janus Kinase 2 (JAk2), Tyrosine Kinase 2 (TYK2) and Signal Transducer and Activator of Transcription 3 (STAT3) signalling pathway that increases IL-17A production.[98] IL-17A also acts as a homodimer or heterodimer with IL-17F to activate the Nuclear Factor-κB (NFκB) pathway, which is

a transcription factor for inflammatory cytokines, chemokines and AMPs.[99] It has been proven by several studies that polymorphism in IL-23R implicated in the pathogenesis of psoriasis.[100-102]

6.4 | T helper 22 (Th22) and skin defence

Th22 is a subset of CD4^{+} T cells that participates in normal skin defence by the production of IL-22, TNF-α and IL-13 cytokines.[103] These adaptive immune cells induce the inflammatory cytokines and antimicrobial peptides production via keratinocytes. Th22 is differentiated by activated DCs through Aryl Hydrocarbon Receptor (AHR), IL-23, IL-6 and TNF-α.[104] These cells are also identified by the chemokines receptors of CCR4, CCR6 and CCR10 that are involved in the homing to the skin.[105] Although, Th22 characterized by IL-22 secretion increases in many inflammatory and autoimmune diseases, including psoriasis, lichen planus, and vitiligo.[33,106-108] This cytokine also up-regulates the production of MMP1 and MMP3 from keratinocytes that leads to tissue destruction.[109-111]

6.5 | CD8^{+} T lymphocytes: Cytotoxic T cells

The major role in cell death and tissue destruction in psoriasis, lichen planus and vitiligo are caused by CD8^{+} T cells.[38,112,113] The most infiltrated lymphocytes to the skin of patients with vitiligo and psoriatic arthritis are CD8^{+} T cells and the numbers of cytotoxic CD8^{+} T cells in the blood of patients is higher than the healthy persons.[114,115] There is a direct relationship between inflammation induced by Th1 cells and activation of cytotoxic CD8^{+} T lymphocytes. Th1 has a pivotal role in priming keratinocytes to CD8^{+} T cells through enhancing MHC class I, as well as IFN-γ production.[69] Also, S100A protein that is released from keratinocytes in response to extracellular stimulation and serves as an epidermal signal transduction mediator is found to induce the cytotoxicity of activated CD8^{+} T cells.[38] It also enhances the activation of NFκB, Nucleotide-binding Oligomerization Domain-Leucine Rich Repeat (NOD-LRR) and Pyrin domains-containing Protein 3 (NLRP3) and production of the pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α. Furthermore, S100A increases the number of keratinocytes and melanocytes under stress conditions and up-regulates the chemokine of CXCL16, which recruits the CD8^{+} T cells.[116,117] After Antigen (Ag)-MHC recognition, CTLs participate in the induction of keratinocyte, melanocyte and basal epithelial cell apoptosis with three main mechanisms including FAS- FAS Ligand (FASL), TNF- TNF Receptor (TNFR) and Granzyme.[64,65,118,119]

Binding of FASL (CD178) to FAS (CD95) on keratinocyte, melanocyte and basement membrane cells causes the apoptosis pathway. FAS-FASL interaction recruits the Fas-Associated protein with Death Domain (FADD) cytosolic adapter which is bound to caspase-8 and induces a death-inducing signalling complex called DISC. The DISC complex activates caspase-3, which induces the Caspase-Activated DNase[120] activation. CAD enters the cell nucleus and destroys the DNA.[121]

Secreted TNF binds to TNFRI in skin cells and induces cell death upon activation of the caspase cascade. This receptor also breaks down the pro-apoptotic protein of BH3 Interacting-Domain Death Agonist to truncated BID (tBID), that interacts with the pro-apoptotic BH3 only family (BAK and BAX) and activates the mitochondrial pathway of cell death.[122]

CD8^{+} T cells perforate the membrane of the target cell by releasing Perforin which facilitating the accession of Granzyme into the cytosol. Granzyme induces cell death through activation of caspases 3 and caspases 7 and subsequently the activation of the mitochondrial pathway of cell death by breaking BID into the tBID.[123]

7 | FDA-APPROVED MONOCLONAL ANTIBODIES IN TREATMENT OF PSORIASIS, LICHEN PLANUS AND VITILIGO

In the last years, an increasing number of monoclonal antibodies (called biological therapies) have entered into the clinic mainly for the treatment of psoriasis with a very good clinical response and safety profile. The concept is based on specific targeting of key playing cytokines in the immunopathology of autoinflammatory skin diseases specifically psoriasis. Several studies were illustrated the remarkable development in the treatment of chronic autoinflammatory skin disorders including psoriasis, lichen planus and vitiligo. Currently, FDA (American Food and Drug Administration) and EMA (European Medicines Agency) approved biological therapies in psoriasis are listed in Table 3. Etanercept, infliximab, certolizumab pegol and adalimumab are all blockers of TNF-α and being the first monoclonal antibodies approved for the treatment of psoriasis with very good efficacy also in psoriatic arthritis.[124,125]

Ustekinumab, a monoclonal antibody directed against p40 subunit of both interleukin IL-12 and IL-23 (blocking both of these cytokines) has been very successful and safe for the treatment of plaque psoriasis and psoriasis arthritis.[126] Recently, IL-17 blocking antibodies ixekizumab, secukinumab and brodalumab have all demonstrated very rapid and stable clinical response in psoriasis and two of them

TABLE 3 FDA/EMA- approved and clinical Trial Monoclonal Antibodies for treatment of psoriasis, lichen planus and vitiligo

Monoclonal antibody	Type	Target	Adverse reactions	Disease	Developmental status (Year)
Etanercept	Human p75 TNF-α Receptors coupled to Human Fc fragment	TNF-α	Injection site / Upper respiratory tract infections / Headache / Fatigue	Lichen Planus / Psoriasis / Vitiligo	Clinical trial phase / Approved / Clinical trial phase
Infliximab	Chimeric Monoclonal Antibody[84]		Upper respiratory tract infections / Skin infections- Headache	Psoriasis	Approved
Adalimumab	Human mAb		Injection site reactions / Headache / Fatigue	Psoriasis	Approved
Certolizumab pegol	Humanized Mouse Fab Fragment		Injection site reactions / Upper respiratory tract infections / Urinary tract infection	Psoriasis	Approved
Secukinumab	Human mAb	IL-17A	Upper respiratory tract infection / Cutaneous fungal infections	Lichen Planus / Psoriasis	Clinical trial phase / Approved
Ixekizumab	Humanized mAb		Injection site reactions / Upper respiratory tract infections / Cutaneous fungal infections	Psoriasis	Approved
Bimekizumab	Humanized mAb	IL-17A & IL-17F	Injection site reactions / Cutaneous fungal infections	Psoriasis	Clinical trial phase
Brodalumab	Human mAb	IL-17 Receptor	Upper respiratory tract infections / Fungal infections / Neutropenia / Arthralgia / Headache / Fatigue / Myalgia	Psoriasis	Approved
Guselkumab	Human mAb	IL-23 p19	Upper respiratory infections / Headache	Psoriasis	Approved
Tildrakizumab	Humanized mAb		Upper Respiratory tract infections	Psoriasis	Approved
Risankizumab	Humanized mAb		Upper Respiratory tract infections / Headache / Fatigue	Psoriasis	approved
Mirikizumab	Humanized mAb		Injection site reaction / Upper Respiratory infections	Psoriasis	Clinical trials phase
Ustekinumab	Human mAb	IL-12/IL-23	Upper Respiratory tract infections / Headaches / Fatigue	Psoriasis	Approved

ixekizumab and secukinumab are also approved for the treatment of psoriasis arthritis.[127] The newest class of biologics for the treatment of psoriasis are p19 blocking antibodies targeting specifically IL-23 without interfering with IL-12 signalling. These group, namely risankizumab, guselkumab, tildrakizumab are recommended in moderate to severe psoriasis patients not responding to conventional systemic treatments and/or phototherapy.[128] There are currently no approved biological therapies for lichen planus and vitiligo but case reports and clinical studies show that some of these might be beneficial for the treatment of these diseases.

8 | CONCLUDING REMARKS

Immunotherapy is one of the leading treatments of immune-mediated disorders such as skin-related autoimmunity. Due to the pathogenesis resemblance of psoriasis, lichen planus and vitiligo diseases, they can be targeted as a convenient candidate for immunotherapy. Meanwhile, the researches on the mechanism of T cell-mediated immune responses indicate the importance of T lymphocytes in the immunopathogenesis of psoriasis, lichen planus and vitiligo. Th1, Th9, Th17, Th22 and CTL are the main contributors to the immunopathogenesis of these diseases. Therefore, the hallmark proof and inhibition of intricated signalling pathways including IL-17/IL-21/IL-23, IFN-γ and TNF-α can open a new horizon in the immunotherapy of these immune-dermatological disorders. Taken together, these cytokines are the appropriate molecular targets for novel and complementary therapies involved in the reduction of irreparable damage to patients with skin autoimmune disorders, in the future.

CONFLICT OF INTEREST
No potential conflict of interest was reported by the author(s).

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Research data are not shared.

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