Cytokine and Growth Factor Reviews 45 (2019) 35–44

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Emerging role of immune cell network in autoimmune skin disorders: An update on pemphigus, vitiligo and psoriasis

Dayasagar Das[a,1], Shamima Akhtar[a,1], Santosh Kurra[a], Somesh Gupta[b], Alpana Sharma[a,*]

[a] Department of Biochemistry, All India Institute of Medical Sciences, AIIMS, New Delhi, India
[b] Department of Dermatology and Venereology, All India Institute of Medical Sciences, AIIMS, New Delhi, India

ARTICLE INFO

Keywords:
Autoimmune skin disease
Pemphigus
Vitiligo
Psoriasis
Immune cell network
Immune checkpoints
Tissue-resident memory cells (TRMs)

ABSTRACT

Autoimmune skin diseases are a group of disorders that arise due to a deregulated immune system resulting in skin tissue destruction. In the majority of these conditions, either autoreactive immune cells or the autoantibodies are generated against self-antigens of the skin. Although the etiology of these diseases remains elusive, biochemical, genetic, and environmental factors such as infectious agents, toxins damage the skin tissue leading to self-antigen generation, autoantibody attack and finally results in autoimmunity of skin. Immune dysregulation, which involves predominantly T helper 1/17 (Th1/Th17) polarization and the inability of regulatory T cells to regress immune response, is implicated in autoimmune skin diseases.

The emerging roles of immune cells, cytokines, and chemokines in the pathogenesis of common autoimmune skin diseases like pemphigus, vitiligo, and psoriasis are discussed in this review. The main focus is on the interplay between immune cell network including the innate and adaptive immune system, regulatory cells, immune checkpoints and recently identified tissue-resident memory cells (TRMs) in disease pathogenesis and relapse. We also attempt to highlight on the immune mechanisms common to these diseases which can be targeted for designing novel therapeutics.

1. Introduction

Autoimmune skin disease pertains to dysregulation of the immune system resulting in autoantibody formation against skin self-antigens. Although the etiology of the disease remains elusive, biochemical, genetic and environmental factors act as a trigger for the autoantibody formation and disease initiation. There is a steady rise in autoimmune skin diseases in recent years. Among them, psoriasis afflicts 2–3%, vitiligo affects approximately 0.5% of the population while pemphigus affects around 0.5–30 cases per million globally [1]. In the Indian subcontinent, the incidences of common autoimmune skin diseases are highest in India. The prevalence of psoriasis is 4.78%, vitiligo is 0.71%–2.64%, and Pemphigus is 4.4–7.2 per million cases [2–6].

In skin resides cells of both innate and adaptive immune system which altogether makes it an immune organ and not just a barrier. The outermost epidermal layer consists of mainly keratinocytes, and few melanocytes, T lymphocytes, and Langerhans cells (LCs). The middle dermal layer is enriched with dendritic cells (DCs), natural killer (NK) cells, macrophages, gamma delta (γδ) T-cells, and innate lymphoid cells (ILCs) along with blood and lymph vessels. Upon pathogen attack, skin immune cells of different compartment work in a regulated and coordinated manner to eliminate the pathogen and maintain the barrier integrity. Nonetheless,

Abbreviations: Th, T helper; LC, langerhans cell; DC, dendritic cell; NK, natural killer cells; γδ, gamma delta; ILC, innate lymphoid cells; TRM, tissue-resident memory cells; DSG, desmoglein; APCs, antigen presenting cells; IL, interleukin; IFN, interferon; Tfh, T follicular helper; PV, pemphigus vulgaris; PF, pemphigus foliaceous; Tregs, regulatory T cells; TGF, transforming growth factor; TNF, tumor necrosis factor; OPN, osteopontin; CTL, cytotoxic T lymphocytes; Bregs, regulatory B cells; 4-TBP, 4-tertiary butyl phenol; MBEH, monobenzyl ether of hydroquinone; XBP1, X-box binding protein 1; UPR, untranslated protein response; pDC, plasmacytoid dendritic cell; iNKT, invariant NKT cells; TRP-1, tyrosinase-related protein-1; GM-CSF, granulocyte monocyte colony stimulating factor; HSP70i, Inducible heat shock protein 70; BSA, body surface area; AHR, aryl hydrocarbon receptor; VDA, vitiligo disease activity; NB-UVB, narrowband ultraviolet; TIM, T cell immunoglobulin- and mucin-domain-containing molecules; Gal, galectin; PD-1, programmed cell death -1; AMP, antimicrobial protein; HBD-2, human-β-defensin-2; PBMCs, peripheral blood mononuclear cells; TLRs, toll-like receptors; NETs, neutrophil extracellular traps; MCETs, mast cell-extracellular traps; Mo-MDSCs, monocytic myeloid-derived suppressor cells; MMP, matrix metalloproteinases; Gro, growth-related oncogene; CMKLR1, chemokine-like receptor1; PASI, psoriasis area and severity index

* Corresponding author at: Department of Biochemistry, Room no. 3015, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi, 110029, India.
E-mail address: dralpanasharma@gmail.com (A. Sharma).

[1] Equal contributions.

https://doi.org/10.1016/j.cytogfr.2019.01.001
Received 11 January 2019; Accepted 18 January 2019
Available online 08 February 2019
1359-6101/

when skin immune system targets its own antigens and initiates destruction of the target cell, autoimmunity develops [7].

In this review, new developments in the immune mechanism of common autoimmune skin disorders i.e. pemphigus, vitiligo, and psoriasis are discussed. We scrutinize the literature pertaining to the innate, adaptive, and regulatory immune cell network, immune checkpoints as well as tissue-resident memory cells (TRMs) in these diseases.

2. Pemphigus

Pemphigus, an autoimmune blistering mucocutaneous disease, produces IgG autoantibodies mainly against autoantigens, Desmoglein-1 (DSG1) and Desmoglein-3 (DSG3), even though the roles of other autoantigens are also implicated in different studies. The pathological hallmark of pemphigus is "acantholysis" which is autoantibody driven disruption of keratinocyte adhesion in the skin and mucosal membrane. A plethora of factors such as genetic, drugs, hormones, environment, viral infections, etc. are reported to trigger autoantibody formation by initially disorganizing the keratinocyte cell-cell contact and exposing the DSGs. Exposed DSGs are then identified by epidermal dendritic-like LCs as antigens which present it to T-cells (Fig. 1) [8,9]. A deregulated cell-mediated immune response is exhibited upon exposure to DSG's, the exact reason for which remains obscure. Both the arms of the immune system i.e. innate and adaptive are involved in the above-mentioned pathogenesis of pemphigus. Innate immune system that used to be considered as early and the non-specific component of immune system shows diversity and its involvement in pemphigus is discussed below.

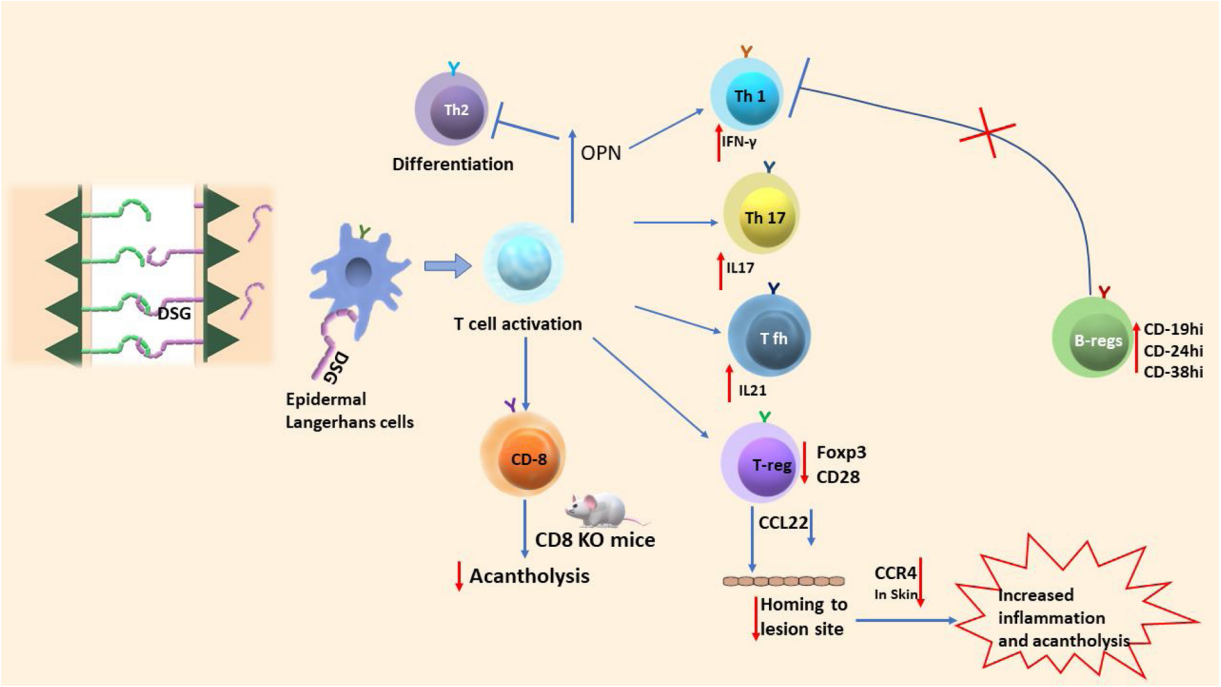

Fig. 1. Immunologic network underlying Pemphigus: Exposed desmogleins (DSGs) identified by epidermal LCs present the antigen to T cells leading to T cell activation and expansion of antigen specific T cells. Elevated OPN levels helps in differentiation of activated T cells towards Th1 type while suppressing Th2 type. Further, cytokines in the microenvironment helps differentiation of activated T cells towards T effector subsets Th1, Th17, and Tfh cells. Reduced expression of FOXP3 and co-stimulatory molecule CD28 on Tregs leads to their decreased proliferation and differentiation. Chemokine receptor-ligand CCL22 – CCR4 is decreased in skin which reduces Treg homing to inflammation site. Bregs become defective as they are unable to suppress IFN-γ secretion from Th1 cells. Eliminating CD8 + T cells reduces pemphigus due to less acantholysis.

2.1. Innate immune system

The function of innate immune system in pemphigus pathogenesis is not much dissected probably because innate cells are rarely detected in lesional skin. In a preliminary study, co-culturing CD4 + T helper (Th) cells and CD56 + CD3- NK cells from Pemphigus patients along with DSG-3 peptides led to proliferation of CD4 + T cells indicating NK cells acts as antigen presenting cells (APCs). NK cells stimulated CD4 + T cells to secrete proinflammatory cytokines interleukin (IL)-8, IL-6, and interferon (IFN)-γ implicating its role in pemphigus pathogenesis [10]. Our group recently reported that, γδ-T cells, an important player of the innate immune system, are detected in pemphigus. High IFN-γ (Th1 type) and low IL-4 (Th2 type) secreting γδT-cells are detected in patient circulation. Elevation of γδT-cells secreting both IFN-γ and IL-4 in pemphigus patients indicates the plasticity of these cells to maintain high autoantibody titers [11].

2.2. Adaptive immune system

2.2.1. CD4 + T helper cells

A cognate T-cell-B-cell interaction is necessary for autoantibody production by autoreactive plasma cells. High titers of autoantibodies are detected in pemphigus patients which correlate well with the disease activity. Presence of autoreactive CD4 + T cells is well documented and reviewed elsewhere [12]. Before the establishment of newly discovered Th cells such as Th17, Th9, Th22, T follicular helper cells (Tfh) in immune response, earlier our group had investigated the Th1/Th2 cytokines in pemphigus. Th2 (IL-10, IL-4) cytokines are elevated in Pemphigus vulgaris (PV) and foliaceous (PF) patients serum while Th1 (IFN-γ and IL-2) cytokines are decreased in the study [13]. Nevertheless, our group and others have established activation and elevation of IL17-secreting Th17 cells with concomitant decrease in FOXP3 + regulatory T cells (Tregs) in pemphigus patients [14–18]. Besides, an involvement of Tfh cells in pemphigus is also indicated. IL-21 secreting Tfh cells were augmented in patient's circulation and infiltrated the lesional skin [17,18]. A single study examined all the subsets of Th cells and observed elevation of inflammatory cytokines IFN-γ (Th1), IL-17, and IL-23 (Th17) with simultaneous decrease in IL-10

indicating a Th1/Th17 response in Pemphigus (Fig.1). Several pro and anti-inflammatory cytokines (TNF-α, IL-6, IL- 1β, IL-2, IL-9, IL-12, IL-4, transforming growth factor (TGF)-β, and IL-33) levels remain unchanged in these patients. Accordingly, chemokine CXCL8 was high while Th1/Th2 chemokine, IP-10, and CCL11 were decreased; CCL2, CCL5, and CCL3 remain unchanged. In skin lesions of these patients also inflammatory cytokines IL-6 and CXCL8 were elevated and IL-2 was reduced indicating a Th1/Th17 response which corroborated positively with disease activity [19]. Association of Th1/Th17 type with early and late-stage disease remains to be investigated.

Cytokine Osteopontin (OPN), an early cytokine of Th1 type, augments production of IFN-γ, IL-12 and decreases IL-10 production [20]. Similar to other autoimmune disorders, in pemphigus also, OPN production is elevated which indicates a Th1 response, a failure of which might elicit a Th2 response (Fig. 1) [21]. Taken together, activation of Th1/Th17/Tfh and down regulation of Treg immune response in pemphigus is strongly indicated.

2.2.2. Regulatory cells

Regulatory T cells, predominantly CD4+FOXP3+ cells are critical players in controlling immune responses. They suppress APC function, B-cell differentiation towards plasma cell, activated CD4 + Th cells, and cytotoxic T lymphocyte (CTL) granule release by secreting immunomodulatory cytokines such as IL-10 and TGF-β [22]. Interestingly, their numbers are reduced in pemphigus which creates an imbalanced immune response [14–16]. CD28, a co-stimulatory molecule, is necessary for Treg activation and successive suppressive function [23]. Any fault in the binding of CD28 molecule with its ligand CD80/86 can have inversed regulatory effect. A high CD28 expression on Th cells and a low expression on Tregs implicates a defective activation and proliferation of Tregs in the circulation of patients (Fig.1) [24]. In vivo expansion of Tregs considerably reduced the DSG3-specific T-cell responses as well as DSG3-specific IgG production [25]. Our lab had reported that chemokine receptor pair for Treg homing, CCR4-CCL22 is lowered leading to homing defect at lesional sites. This defective receptor-ligand edge may have become futile to suppress the inflammatory microenvironment produced by Th17 cells in lesions thus promoting inflammation and contributing to the immunopathogenesis of pemphigus (Fig.1) [14].

In pemphigus patients, activated B cells act as pathogenic regulators by secreting anti-DSG3 autoantibodies. B regulatory cells (Bregs) are able to down regulate immune responses in mice and humans by secreting IL-10, TGF-β and expressing FOXP3 [26,27]. A high CD19+CD24hiCD38hi Bregs number is seen in pemphigus patients which is higher in active patients than remittent. IL-10-producing Breg cells markedly increase upon stimulation in patients and in healthy controls but only control Bregs suppressed IFN-γ expression and Th1 immune response. Bregs from patients had 3 fold reduced suppressive function (Fig.1) [28]. Further studies in future will evaluate the potential of these regulatory cells to control the inflammatory immune response in pemphigus.

2.2.3. Cytotoxic $CD8^+$ T cells

A great number of studies have shed light on CD4 + T cells role in the pathogenesis of pemphigus while the role of CD8+ cytotoxic cell is less explored possibly due to the lower number of CD8+ cells in the skin lesions. CD8 knockout mice had reduced incidences of pemphigus indicating its role in disease progression (Fig.1). The role of this small subset of T-cells needs to be further explored [29].

3. Vitiligo

Vitiligo is an autoimmune disorder where epidermal melanocytes are targeted and destroyed by various ways leading to irregular depigmentation of the skin. Biochemical, neural, and autoimmune mechanisms partly explain the mechanisms for the degeneration of melanocytes in vitiligo. The biochemical trigger for vitiligo is mainly oxidative stress induced by different chemicals [30]. 4-tertiary butyl phenol (4-TBP) and monobenzyl ether of hydroquinone (MBEH), the chemical triggers for vitiligo up-regulates the untranslated protein response (UPR) in melanocytes (Fig. 2). Transcription factor X-box binding protein 1 (XBP1), a UPR components, is activated which

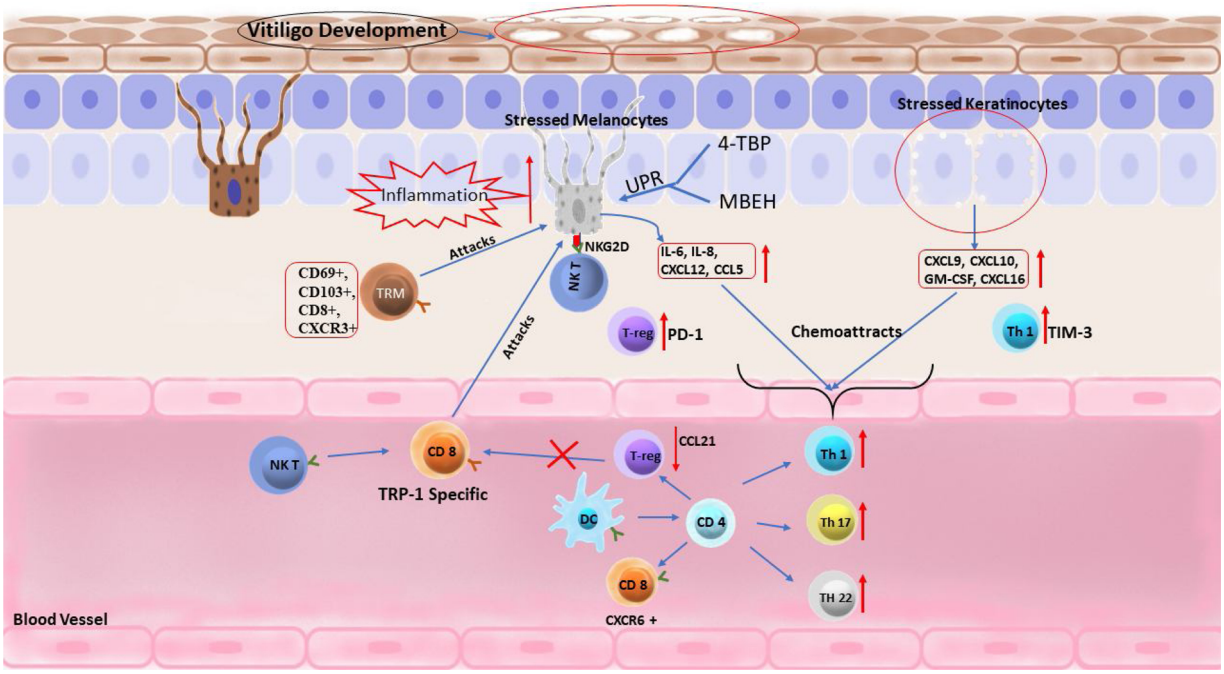

Fig. 2. Immune mechanisms involved in vitiligo: Chemical triggers (4-TBP and MBEH) induced untranslated protein response (UPR) upregulates proinflammatory cytokines and chemokines production in melanocytes. LCs and DCs are APCs inducing T cell activation. NKT cells binds to its receptor NKG2D to induce antigen specific CD8 T cell proliferation which attacks melanocytes. T helper cells differentiate into Th1, Th17 and Th22 which maintains inflammatory milieu. Tregs are unable to regulate heightened inflammation due to reduced number and defective homing. TRMs aid in disease recurrence by secreting proinflammatory cytokines upon restimulation. Negative immune checkpoint PD-1 is upregulated in Tregs while TIM-3 is upregulated in Th1 cells contributing to inflammation.

subsequently increases production of proinflammatory cytokines IL-8 and IL-6 by the melanocytes. XBP1 inhibitors reduced IL-8 and IL-6 production induced by phenols [31]. Taken together, exposure to environmental stressors causes an insult to melanocytes which then produce cytokines associated with activation of an immune response finally leading to melanocyte loss and depigmentation. Autoimmune responses also play significant role in establishment and progression of vitiligo described below.

3.1. Innate immune response

Transcriptome analysis of vitiligo skin indicated activation of innate immune cells [32]. CD1a + CD207+ LCs are increased in lesional skin with structural modifications such as increased dendrite length and number reflecting its activation. Similarly, the dermal DCs (CD1a + CD207-) are also increased in vitiligo lesions [33]. CD11c + myeloid dermal DCs and CD207+ LCs are enriched at the progressing interface of the vitiligo biopsies. DC-LAMP + and CD1c + sub-populations of dermal DCs increased remarkably in the progressing interface and lesional skin. Activated inflammasomes along with increased IL-1ß mRNA in LCs of lesional vitiligo skin, indicates the potential of LCs to drive Th17 activation. [34]. Contradictorily, epidermal immune cell populations such as endogenous T lymphocytes, LCs, and γδ T-cells were not necessary for the disease progression in a mouse model of vitiligo [35].

NKT cells and plasmacytoid DCs (pDCs) play a role in vitiligo pathogenesis [32,36,37]. NKT cells (CD3-NKG2D+) with increased cytolytic activity are elevated in vitiligo lesions [32]. In contrast, invariant NKT cells (iNKT), which is implicated in autoimmune disease, is drastically reduced in non-segmental vitiligo suggesting a role in disease pathogenesis [38]. Further, in experimental vitiligo, contrasting effects of two NK receptors is demonstrated in the development of self-reactive CD8 + T cell response. Binding of melanocyte antigen, tyrosinase-related protein-1 (TRP-1) to NKG2D ligand (Rae-1e or H60) elicited potent CD8 + T-cell responses against TRP-1 causing development of vitiligo. Complexing of TRP-1 with the natural ligand for the NK cell receptor 2B4,CD48, leads to decreased formation of TRP-1-reactive CD8 + T-cell responses, thus reducing development of vitiligo (Fig.2) [37].

Keratinocytes of patients produce CXCL9 and CXCL10 which are chemoattractant for DCs besides other immune cells [35]. Moreover, granulocyte monocyte colony stimulating factor (GM-CSF), known to affect myeloid DC proliferation and maturation is upregulated in the serum of vitiligo patients [36]. pDCs are IFN-γ producing cells which correlated with the expression of the type I IFN-inducible ligand CXCL9 in lesional skin which correlated well with disease activity. This in turn correlated with the recruitment of immune cells expressing CXCR3 [35,38]. In vitiligo-prone Pmel-1 mice, inducible Hsp70 (HSP70i), a stress-related protein, accelerated depigmentation, and phenotypic changes in DC subpopulations [39]. Together, epidermal and peripheral DCs are associated with disease initiation probably by being APCs whereas NK cells regulate the disease progression.

3.2. Adaptive immune response

3.2.1. Cytotoxic CD8+ T cells

Peripheral expansion of melanocyte-specific CD8+ T cells occurs in vitiligo [40]. Accordingly, tissue infiltrate of lesion consists mainly of cytotoxic CD8+ T cells than CD4+ Th cells [41,42]. Infiltration of CD8+ T cells is mainly due to cytokines and chemokines secreted by the stressed keratinocyte and melanocytes.

Chemokine CXCL16 expression is augmented in keratinocytes under oxidative stress and mediates migration of CXCR6+CD8+ T cells isolated from vitiligo patients (Fig.2). Skin infiltration of CXCR6+CD8+ cells led to the loss of melanocyte in lesions [43]. Moreover, melanocytes of early lesions have considerable elevation in levels of chemokine CXCL12 and CCL5 which concurred with penetration of skin with APCs and T cells. In a mouse model of vitiligo, transplantation of CXCL12+ and CCL5+ melanocytes resulted in preferential recruitment of CD11c + APCs and CD8+ T cells to CXCL12- and CCL5-expressing melanocytes, epidermal melanocyte loss, and development of vitiligo-like lesions [44]. Our research group has shown that the success rate of melanocyte transplantation in patients is inversely proportional to the number of CD8 cells and CD45RO cells in the lesion but doesn't depends on the number of CD4+ T cells, CD 45RA and FOXP3+ Tregs cells [45]. In the essence, infiltration of the cytotoxic CD8 T cells might be responsible for the melanocyte destruction in vitiligo.

3.2.2. CD4+ T helper cells

Increasing number of studies has reported the role of T helper cells such as Th17 cells in the disease progression of vitiligo. Elevated Th17 cell frequencies are observed in vitiligo patients [34,46–48]. RORγt, the transcription factor for Th17 cells, as well as transcription and protein levels of Th17 cytokines, IL-17 A, IL-22, and IL-21 were increased remarkably in patients [34,46–49]. Increased Th17 cell frequency positively correlated with the body surface area (BSA) of the lesion [47]. Further, Th17 cells were present in the leading edge of the lesional skin [34]. Aryl hydrocarbon receptor (AHR) transcription factor, the master regulator of Th22 cells, was significantly elevated in vitiligo patients implicating contribution of Th22 cell to abnormal immune responses seen in vitiligo [50]. Additionally, the numbers of Th1 cells were increased considerably in patients [47,48]. Although IFN-γ levels are unchanged in patients, the transcription factor for Th1 activation, T-bet was increased at transcription level indicating activation of Th1 cells [48]. Our group had shown an elevation of IL-2, a Th1 cytokine in patients [49]. In one study, Th2 cell number, their transcription factor GATA-3, and cytokine IL-4 were comparable between patients and healthy controls (Fig.2) [48]. Contrarily, a study on Indian patients showed an elevated IL-4 level [49] indicating that the involvement of Th2 in vitiligo pathogenesis is debatable.

Natural regulatory T cells (nTregs), the suppressor CD4+ Th cells is decreased in vitiligo patients but increased in perilesional skin of the patients. Nonetheless, peripheral Tregs were impaired in their function as they were unable to suppress the proliferation and cytolytic capacity of autologous CD8 + T cells, ultimately leading to hyperactivation of CD8+ CTLs in vitiligo [41]. Peripheral CD4+ FOXP3+ Treg cells, CCL21 (chemokine for Treg homing) and TGF-β1 were decreased in patients which correlated negatively with vitiligo disease activity (VIDA) score and BSA (Fig.2) [49,51,52]. However, one study did not find any difference in Treg cells between patients and controls. Treg cell number, its transcription factor FOXP3 and cytokine TGF-β1 were comparable between the groups [34]. Together, it indicates that similar to pemphigus, the inflammatory Th cells are elevated in vitiligo with concomitant decrease in Treg cells which became defective.

Even though CD8+ CTL attack causes melanocyte loss in vitiligo, will reversing the Th cell phenotype in patients decrease the melanocyte loss is yet to be answered. Narrowband ultraviolet (NB-UVB), an effective therapy for generalized vitiligo, is known to modulate local or systemic immune response. The treatment down-regulates immune attack against the melanocytes and simultaneously stimulates melanocytes to migrate to the epidermis and synthesize melanin. Using this treatment modality, our group has shown that IL-10 and TGF-β is increased in NB-UV treated patients while IL-13 and IL-17 A are elevated in untreated patients as compared to treated patients. NB-UVB mediates its action by reducing Th17/Th1/Th2 and increasing Treg cytokines which might then suppress the cytolytic activity of CD8+ T cells [53]. Nevertheless, the effect of the treatment on the functionality of Tregs and cytotoxic CD8+ cells needs to be elucidated.

3.3. Immune checkpoints

Biologically several molecules exist in immune system that regulates

the over expressing immune response thereby maintaining the immune homeostasis. These molecules are collectively known as immune checkpoints. Recently these molecules are being utilized to alter the immune response in many diseases including cancer.The T cell immunoglobulin- and mucin-domain-containing molecules (TIM)-1 is an immune checkpoint, expressed on activated Th2 cells while TIM-3 is expressed on Th1 cells. Our group had shown that a higher percentage of circulating CD3 + CD4 + TIM3 + T cells which positively associated with percentage BSA involvement in patients. Furthermore, augmented transcription of TIM-3 and its ligand galectin (Gal)-9 as well as characteristic migration pattern of TIM-3 + immune cells in lesional and perilesional skin suggested that TIM-3 + immune cells might be involved in melanocyte destruction (Fig.2) [54].

Programmed cell death 1 (PD-1) is another immune checkpoint which inhibits immune response by binding to its ligands, PD-L1 and PD-L2. In Pmel-1 vitiligo mice treatment with PD-L1 fusion protein suppressed depigmentation as well as caused enrichment of Tregs in the skin, spleen and in circulation suggesting PD-L1 protein therapy impedes the immune response and reverses depigmentation in Pmel-1 vitiligo mice [55]. However, in spite of decreased Tregs, PD-1 + Tregs are increased in generalized vitiligo suggesting an involvement of PD-1/PD-L1 pathway in Treg exhaustion (Fig.2) [51]. Alteration in immune responses using PD-1/PD-L1 blockers in vitiligo needs to be investigated which can have great potential for novel therapeutics in disease management in future.

4. Psoriasis

Psoriasis is a T-cell mediated autoimmune disease characterized by increased keratinocyte proliferation leading to the formation of distinct erythematous plaques with large scaling. Although the etiology of the disease is unclear, genetic and environmental factors are thought to be the reason behind abnormal immune response in psoriasis patients. A typical feature of psoriatic skin is high expression of innate antimicrobial proteins (AMP) such as S100 A and human-β-defensin-2 (HBD-2) [56,57]. Koebnerisin (S100A15) and psoriasin (S100A7) over expressed in the epidermal psoriatic lesions, acts as chemoattractant for immune cells (Fig. 3). These proteins induce proinflammatory cytokines such as IL-8, IL-6, IL-1β, and TNF-α, in peripheral blood mononuclear cells (PBMCs). Upon NB UV-B treatment, Koebnerisin levels are suppressed in PBMCs of psoriatic patients thus making it a therapeutic response marker in psoriasis [58].

4.1. Innate immune response

4.1.1. Neutrophils

In psoriasis, Toll-like receptors (TLRs) bind to AMPs by which the APCs get stimulated and secrete proinflammatory chemokine CXCL16 [59,60]. CXCL16 mediates migration of neutrophils by decreasing stiffness and increasing deformation facilitating transmigration through the vessel wall. In a positive feedback loop, IL-8 enhanced CXCL16 production in neutrophils [60]. Upon IL-8 activation, neutrophils secrete neutrophil extracellular traps (NETs) which in turn upregulates HBD-2 in keratinocytes, and psoriatic lesions [61]. IL-17 + neutrophils and mast cells are found at higher densities than IL-17 + T-cells in psoriatic lesions which frequently release IL-17 in the process of forming NETs and mast cell-extracellular traps (MCETs), respectively (Fig.3). IL-23 and IL-1β can induce MCET formation and degranulation of human mast cells [62]. IL-17 F, sharing 50% sequence homology with IL-17 A, is also upregulated in psoriasis and produces an equal intensity of inflammation as IL-17 A [63,64]. Both IL-17 A/F is highly expressed by neutrophils and mast cells [63]. Neutralization of both IL-17 A and IL-17 F reduces neutrophil chemotaxis and psoriasis disease severity more efficiently than IL-17 A alone indicating an equal contribution of IL-17 F in the disease pathogenesis [64].

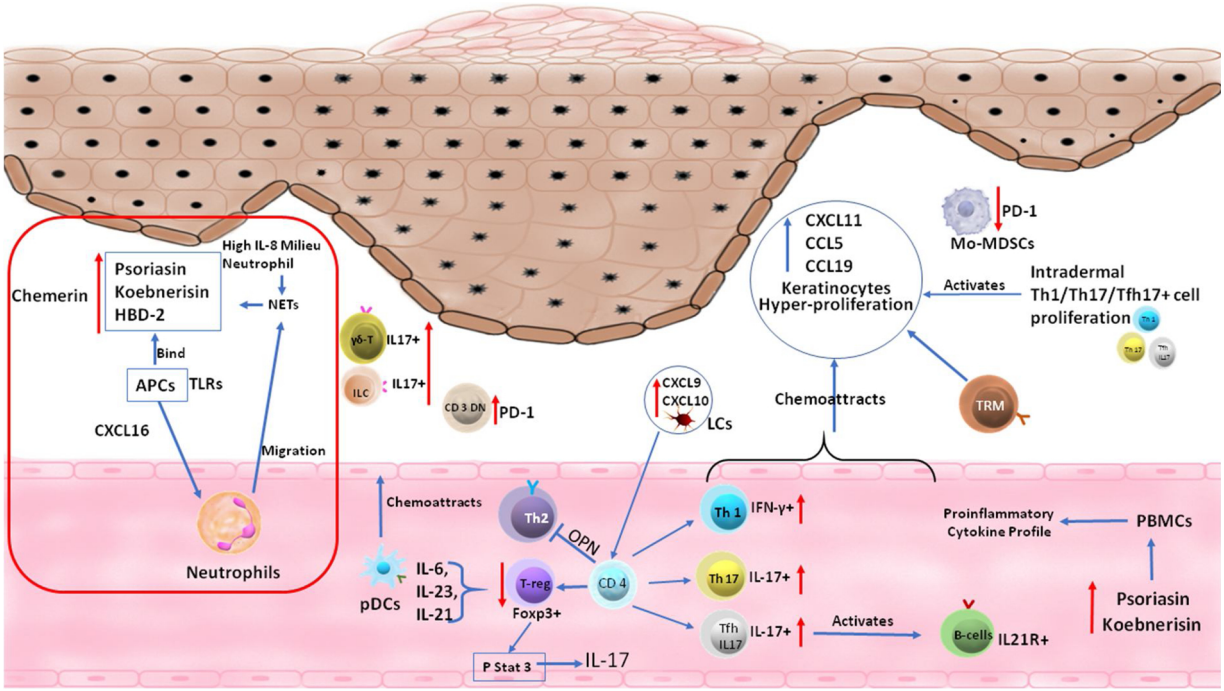

Fig. 3. Immune mechanism of Psoriasis: AMPs are over expressed in skin and circulating leucocytes in psoriasis. TLR on APCs bind to AMPSs and get stimulated and secretes CXCL16. Neutrophils and mast cells are chemoattracted in response to chemokines and cytokines and secrete extracellular traps (ETs). ETs in turn upregulate AMPs in keratinocytes establishing a positive feedback loop and also secrete IL-17. Macrophages are classically activated, DCs, NK cells, ILCs, γδ T cells and activated keratinocytes secretes proinflammatory cytokines and chemokines which adds on to the inflammatory condition. Activated T cells differentiate into subtypes; Th1, Th17, Th9 and Tfh cells. In the inflammatory state, Tregs function is altered and they behave like Th17 cells secreting IL-17. Negative immune checkpoints such as PD-1 and are decreased in Mo MDSCs and PBMCs setting a sustained immune response. TRMS and skin resident γδ- T memory cells produce proinflammatory cytokines upon stimulation thus contributing to disease recurrence.

4.1.2. Macrophages

In experimental psoriasis, model skin seen to be infiltrated with macrophages. In absence of T cells, psoriasis was enhanced with increased inflammation and infiltration with macrophages [65]. Further, CD163+, RFD7+, CD68+, LAMP2+, Stabilin-1+, and MARCO + dermal macrophages which are "classically activated" are increased in the psoriatic lesion and produce inflammatory molecules IL-23p19 and IL-12/23p40 as well as TNF and iNOS [66,67]. Intermediate monocytes (CD14++CD16+) with high expression of co-stimulatory molecule CD86, a marker for "classically activated" macrophage, is present in the skin of psoriatic patients and is associated with increased epidermal proliferation and disease severity [68].

Recently, high levels of CD14+HLA-DRe/low monocytic myeloid-derived suppressor cells (Mo-MDSCs) in peripheral blood psoriatic patients have been reported (Fig. 3). These cells, produce many pro-inflammatory molecules such as matrix metalloproteinases (MMP)-9 and-1, IL8, growth-related oncogene (Gro), and CCL2 [69]. They suppressed CD8 T-cell proliferation less effectively than healthy control [69,70]. In presence of these pro-inflammatory cytokines, psoriatic Mo-MDSCs induces aberrant Treg cell conversion from naive T effector cells, thus affecting the immune system's ability to correctly self-regulate [70].

4.1.3. Dendritic and NK cells

High expression of chemerin in psoriatic skin, a ligand for chemokine-like receptor1 (CMKLR1) expressed on pDCs leads to its selective recruitment to lesion site (Fig. 3) [71]. CD11c+-blood dendritic cell antigen (BDCA)-1-myeloid DCs cells are increased manifold in psoriatic lesional skin and produce simultaneously IL-17 and IFN-γ [72]. Further, LCs expresses chemokine CXCL9 and CXCL10, chemoattractants for T cells, in psoriasis patients [73]. On the other hand, natural killer (NK) cells are present in the lesional skin of psoriasis patients and exhibited reduced degranulation and produced lower levels of the pro-inflammatory cytokines IFN-γ and TNF-α [74].

4.1.4. Other innate immune cells

A distinct subset of proinflammatory cutaneous lymphocyte antigen positive (CLA+) and CCR6 + Vγ9Vδ2 T-cells in blood migrates into perturbed skin and secreteIL-17 A, IL-22 and activates keratinocytes upon TNF-α, IFN-γ, and IL-23 stimulation. In psoriasis, these γδT cells are decreased in peripheral circulation with concomitant increase in lesional skin suggesting their pathogenic role [75]. IL-23 from LC induced production of IL-17 A producing CCR6+ γδT cells as depletion of LCs reduced the IL-17 A producing CCR6+ γδT cells (Fig. 3) [76].

Innate lymphoid cells (ILCs) are lymphoid lineage cells which lack antigen-specific receptors. An increased frequency of IL-22- and/or IL-17A-producing ILCs is noted in psoriatic skin and blood which correlated with disease severity [77]. A recent report mentions that ILCs are activated in response to IL-23 and IL-1β and are decreased following anti-TNFα treatment suggesting dysregulation of ILCs as a contributing factor to psoriasis pathogenesis (Fig. 3) [78].CXCL11 and CCL5, a chemoattractant for IFNγ+ immune cells, is increased in psoriatic lesion as well as in human keratinocyte stimulated by IFNα. This increase is mediated by the phosphorylation of STAT2 in keratinocytes [79]. CCL19, a T-cell chemoattractant, and its receptor CCR7 are produced locally in psoriatic keratinocytes adding to disease pathogenesis [80].

4.2. Adaptive immune response

4.2.1. T cells

In psoriasis, it is hypothesized that the effector T-cells accumulate within lymph nodes from where they migrate into the skin through the blood system. Recently, psoriatic skin is shown to be another source for inflammatory T cells. An intra-dermal proliferation of T cells was noted in psoriatic skin with maximal proliferation in patients with active disease than the patients in remission (Fig. 3). The number of T cells in remission patients was even higher than controls indicating the presence of an immunologic memory [74].

4.2.2. Th1-Th2

Increased activation of CD4+ T lymphocytes is observed in psoriasis. In peripheral circulation high Th1 and low Th2 cells occurs in psoriasis [81]. Remarkably higher IFN-γ, IL-2, IL-10 and lower IL-4 concentration in the serum as well as high expression of T-bet mRNA and reduced expression of GATA-3 mRNA in PBMCs of psoriatic patients suggests the immunopathogenesis of the disease is predominantly Th1-mediated [82–84]. Accordingly, OPN is expressed in PBMCs and skin biopsies [85]. Psoriasis patients in the early course of disease have high expression of the IFN-γ, which shifted towards IL-10 secretion in chronic patients suggesting a possible shift from Th1 to Th2 response as an adaptation of the immune system to down regulate inflammatory Th1 response (Fig.3). Further, tissue expression of both IFN-γ and IL-4 was low in psoriasis but were similar between stable and active disease which correlated weakly with psoriasis area and severity index (PASI) scores implicating a change in cytokines levels is not related with disease activity or severity [83].

4.2.3. Th17

Th17 cells, its transcription factor RORγ and cytokines IL-17 and IL-22 are increased in peripheral circulation and lesions of psoriatic patients [81,82,86,87]. Th17 cell differentiation is mediated by activation of Notch1 signaling as inhibition of Notch1 reduced Th17 cell percentage, RORγ and IL-17 [88]. Unrestricted IL-36 secretion by innate immune cells signals for an increased TCR-mediated proliferation of CD4+ T-cells as well as enhanced secretion of IL-17 A in blood and lesion of psoriasis patients [89]. IL-21 and IL-21+Th17 cells are also elevated in blood and lesions which had a positive correlation with disease severity [82,87]. In vitro, IL-21 stimulation of CD4+ T-cells promotes their differentiation to Th17 cells [87]. Lower levels of IL-27 in blood and lesions of moderate-to-severe psoriasis patients are observed. IL-27 restricts differentiation of CD4+ Th cells to Th17 cells which concomitantly decreases IL-27 secretion [90].

IL-17 A causes an elevation in total intracellular cholesterol in keratinocytes which is necessary for its downstream signaling. Reducing total cholesterol levels by methyl-β-cyclodextrin considerably reduced IL-17 A induced secretion of IL-8, CCL20, and S100A7 from the keratinocytes indicating an association between psoriasis and dyslipidemia [91]. Further IL-17 A induces production of IL-19 in keratinocytes which is further potentiated by TNF-α and IL-22. IL-19 in turn augmented the production of S100A7/8/9 and moderately enhanced IL-1β, IL-20, CXCL8, and MMP-1. IL-19 strengthens IL-17 A action on keratinocytes such as induction of HBD-2, IL-19, IL-23p19, and Th17 cell- and neutrophil-attracting chemokines [92]. Additionally, in keratinocytes IL-17/CIKS signaling leads to hyperproliferation of the cells with attenuated differentiation and neutrophilic microabscess formation. In non-keratinocytes, IL-17 signaling accumulates IL-17-producing γδ T cells in skin [93]. Besides, keratinocytes stimulated with IL-17 also upregulates chemokines which are implicated in the influx of neutrophils (CXCL1, CXCL3, CXCL5, CXCL6, and CXCL8), dendritic cells and memory T cells (CCL20). While keratinocytes stimulated with IL-22, a Th17 cytokine, leads to down regulation of genes associated with keratinocyte differentiation (*Keratin 1, Filaggrin*, *CALML5*) and epidermal modifications [94].

4.2.4. Th9 and Tfh

T cells producing IL-9 are increased in psoriatic lesions indicating that aberrant activation of Th9 cells contributes to disease pathogenesis. Blocking studies revealed that IL-9 is essential for production of IL-9, IFN-γ, IL-17, and IL-13 by skin tropic T cells to maximal level. Furthermore, a majority of the memory Th9 cells are either skin-tropic or are skin-resident [95]. In psoriasis, a higher percentage of circulating Tfh17 (CXCR3-CCR6+) cells is seen having a high correlation with disease severity. Expression of IL-21R on B cells was appreciably increased in psoriatic patients which had a strong correlation with disease

severity and frequency of Tfh17 cells [96]. On the other hand, CXCR5 + PD-1 + Tfh cells were decreased in psoriatic patients. The absolute number of CXCR5 + PD-1 + and CXCR5 + ICOS + Tfh cells increased with disease duration with no relation to disease severity [97].

4.2.5. Regulatory T cells

FOXP3 + expressing Tregs, which are known to suppress the inflammatory immune response, are decreased in psoriasis (74, [81]). Elevated levels of pro-inflammatory cytokines IL-6, IL-21, and IL-23 in the blood of psoriatic patients leads to phosphorylation of STAT3 in Tregs [98,99]. STAT3 phosphorylation in T-cells leads to Th17 differentiation. Accordingly, Tregs isolated from psoriatic patients could produce IFN-γ, TNF-α, and IL-17 [96]. Further, IL-6 induced expression of IL-6Rα expression on Treg cells which exceeded that of T effector cells [98]. Together, in high pro-inflammatory cytokine milieu, psoriatic Tregs behave like Th17 cells and are unable to suppress the T effector activation. Adding STAT3 inhibitor partially restores the suppressive function of Tregs and reduced the expressions of IFN-γ, TNF-α and IL-17 in psoriatic patients (Fig. 3) [99]. Besides, eliminating Treg cells in wild-type mice increased both psoriasis and infiltrating macrophages. Adoptive transfer of FOXP3 + T cells into RAG1 knockout or wild-type mice decreased development of psoriasis as well as macrophage infiltration. Thus, Treg lymphocytes impede the proinflammatory activity of macrophages [65].

4.3. Immune checkpoints

In psoriasis, TCR^+ $CD3^+$ $CD4^-$ $CD8^-$ "double negative" (DN) T and $PD\text{-}1^+$ cells are increased in number and infiltrate the epidermal lesions. These cells exhibit phenotypes commonly seen in effector memory cells, secrete IFN-γ, and fail to proliferate [100]. Accordingly, high expression of negative immune regulatory genes (CTLA4, CD69, and PD-L1) occurs in mild psoriasis compared to severe form [101]. On the contrary, expression of PD-1 and neuropilin-1 (NRP1) but not of human leukocyte antigen G (HLA-G) is reduced in PBMCs of psoriasis patients [102]. Additionally, in psoriasis Mo-MDSCs expressed reduced levels of PD-1 compared to controls (Fig. 3) [70].

5. Tissue-resident and innate immune memory cells

Newly identified subclass of memory T cells, tissue-resident memory T (TRM) cells, are non-circulating and retain in epithelial barrier tissues, including skin for longer duration [103]. Involvement of resident memory T (TRM) cells is implicated in disease recurrence in the same area even after completion of treatment. CD69 + CD103 + CD8 + TRMs were present in both stable and active vitiligo perilesional skin and mainly localized in the epidermis. These TRMs also expressed CXCR3 and produced elevated levels of IFN-γ and TNF-α with moderate cytotoxic activity (Fig.2) [104]. In psoriasis, patient in remission has enriched epidermal CD8 + TRMs expressing CLA antigen, CCR6, CD103, and IL-23R which produced IL-17 A on ex vivo stimulation. Likely, epidermal CD4 + CD103 + TRMs produced IL-22 on stimulation (Fig.3) [105]. Role of TRMs in pemphigus pathogenesis remains to be investigated.

In experimental psoriasis model, IL-17 A/F-producing Vγ4 + Vδ4 + T cells migrate and retain in the dermis for a longer duration after initial stimulation. Antigen exposed Vγ4 + Vδ4 + cells exhibit robust effector functions and a secondary inflammatory response indicating participation of "innate immune memory" in delivering fast and strong immune response upon re-challenge [106]. Role of innate immune memory in disease reappearance in vitiligo and pemphigus needs to be examined.

6. Conclusion

Recently, significant advancement has been made in understanding the role of the immune cell network in autoimmune skin diseases. Some common players in pemphigus, vitiligo and psoriasis pathogenesis are identified such as Th1/Th17 immune response, defective regulatory cells, activated LCs, CD8 + T-cells and TRMs suggesting a common pathway for disease pathogenesis (Fig. 4). Further, different layers of

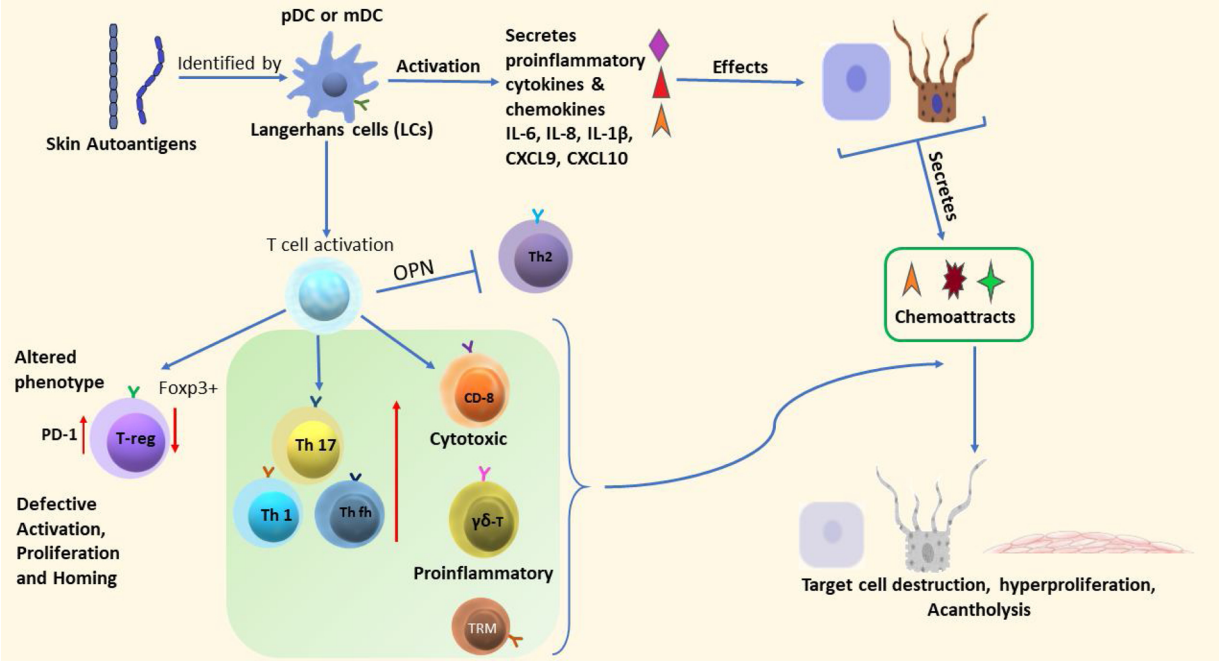

Fig. 4. Unified immune mechanism of common autoimmune skin disease: Skin self-antigens are identified by LCs and dermal DCs which acts as APCs. Antigen binding activates LCs which secrets proinflammatory cytokines and chemokines. This in turn activates keratinocytes which also secrets proinflammatory cytokines and chemokines, thus maintaining the inflammatory state. LCs and dermal DCs present antigen to skin resident and circulating T cells which proliferate and differentiate into Th1, Th17 and Tfh cells. Th1 and Th17 cells maintain the inflammatory state, Tfh cells activate antigen specific B cells to proliferate and produce autoantibodies. Tregs are decreased in circulation due to defective proliferation and in skin due to defect in homing. Tregs phenotype is altered from anti- to pro-inflammatory. CD8 T cells attack the keratinocytes and melanocytes. Antigen specific CD4 and CD8 TRMS produce proinflammatory cytokines upon stimulation thus contributing to disease recurrence.

regulatory cells are identified such as MoMDSCs and iNKT (innate regulatory cells) as well Tregs and Bregs (adaptive regulatory cells) which needs to be investigated in PV, vitiligo, and psoriasis. Even though different treatment regimens have shown to increase Tregs in all the three autoimmune skin diseases, none efficient enough to reverse the disease. This might be due to either role played by other regulatory cells or phenotype change of Tregs due to their plastic behavior in inflammatory microenvironment or both. A detailed knowledge of pathways involved in the dysregulation of innate and adaptive regulatory cells is needed. Further, the role of TRMs is implicated in disease recurrence after treatment completion. Novel therapeutics targeting elevation of innate and adaptive regulatory cells as well as down regulating TRMs would be of great value in treating these diseases. In this maiden comprehensive review, aberration in immune cell network has been highlighted. The detailed understanding of this network and possible interventions may lead to better management of these autoimmune skin diseases.

Funding source

None.

Declarations of interest

None.

References

[1] J.M. Richmond, J.E. Harris, Immunology and skin in health and disease, Cold Spring Harb. Perspect. Med. 4 (2014) a015339.
[2] K.D.A. Pandey, R. Sekhri, Prevalence of psoriasis: an Indian perspective, J. Am Acad. Dermatol. 74 (2016) AB264.
[3] J. Reddy, A survey on the prevalence of Vitiligo in Banglore City, India, Int. J. Pharma Med. Biol. Sci. 3 (2014) 34–45.
[4] S.O.A. Agrawal, S. Gupta, Profile of vitiligo in Kumaun region of Uttrakhand, India, Indian J. Dermatol. 59 (2014).
[5] K.A. Kumar, Incidence of pemphigus in Thrissur district, south India, Indian J. Dermatol. Venereol. Leprol. 74 (2008) 349–351.
[6] D.P.K. Parmar, Prevalence of pemphigus incidence in the Bhuj, Kutch, Gujarat: a cross-sectional study, Int. J. Res. Dermatol. 3 (2017) 478–480.
[7] F. Abdallah, L. Mijouin, C. Pichon, Skin immune landscape: inside and outside the organism, Mediators Inflamm. 2017 (2017) 5095293.
[8] M. Kasperkiewicz, C.T. Ellebrecht, H. Takahashi, J. Yamagami, D. Zillikens, A.S. Payne, M. Amagai, Pemphigus, Nat. Rev. Dis. Primers 3 (2017) 17026.
[9] R. Pollmann, T. Schmidt, R. Eming, M. Hertl, Pemphigus: a comprehensive review on pathogenesis, clinical presentation and novel therapeutic approaches, Clin. Rev. Allergy Immunol. 54 (2018) 1–25.
[10] J.N. Stern, D.B. Keskin, N. Barteneva, J. Zuniga, E.J. Yunis, A.R. Ahmed, Possible role of natural killer cells in pemphigus vulgaris - preliminary observations, Clin. Exp. Immunol. 152 (2008) 472–481.
[11] D. Das, V. Anand, S. Khandpur, V.K. Sharma, A. Sharma, T helper type 1 polarizing gammadelta T cells and Scavenger receptors contribute to the pathogenesis of Pemphigus vulgaris, Immunology 153 (2017) 97–104.
[12] K. Amber, P. Staropoli, M.I. Shiman, G.W. Elgart, M. Hertl, Autoreactive T cells in the immune pathogenesis of pemphigus vulgaris, Exp. Dermatol. 22 (2013) 699–704.
[13] A. Satyam, S. Khandpur, V.K. Sharma, A. Sharma, Involvement of T(H)1/T(H)2 cytokines in the pathogenesis of autoimmune skin disease-Pemphigus vulgaris, Immunol. Invest. 38 (2009) 498–509.
[14] R. Asothai, V. Anand, D. Das, P.S. Antil, S. Khandpur, V.K. Sharma, A. Sharma, Distinctive Treg associated CCR4-CCL22 expression profile with altered frequency of Th17/Treg cell in the immunopathogenesis of Pemphigus Vulgaris, Immunobiology 220 (2015) 1129–1135.
[15] N. Joshi, R.W. Minz, S. Anand, N.V. Parmar, A.J. Kanwar, Vitamin D deficiency and lower TGF-β/IL-17 ratio in a North Indian cohort of pemphigus vulgaris, BMC Res. Notes 7 (2014) 536.
[16] R.C. Xu, H.Q. Zhu, W.P. Li, X.Q. Zhao, H.J. Yuan, J. Zheng, M. Pan, The imbalance of Th17 and regulatory T cells in pemphigus patients, Eur. J. Dermatol. 23 (2013) 795–802.
[17] T. Hennerici, R. Pollmann, T. Schmidt, M. Seipelt, B. Tackenberg, C. Mobs, K. Ghoreschi, M. Hertl, R. Eming, Increased frequency of t follicular helper cells and elevated Interleukin-27 plasma levels in patients with pemphigus, PLoS One 11 (2016) e0148919.
[18] H. Yuan, S. Zhou, Z. Liu, W. Cong, X. Fei, W. Zeng, H. Zhu, R. Xu, Y. Wang, J. Zheng, M. Pan, Pivotal role of Lesional and perilesional T/B lymphocytes in pemphigus pathogenesis, J. Invest. Dermatol. 137 (2017) 2362–2370.
[19] R. Timoteo, Vinicius da Silva, M. Miguel, C.B. Silva, D.A. Da Silva Catarino, J. Rodrigues, V. Sales-Campos, H. Oliveira, CJF, Th1/Th17-related cytokines and chemokines and their implications in the pathogenesis of pemphigus vulgaris, Mediators Inflamm. (2017) 1–9.
[20] M. Inoue, M.L. Shinohara, Intracellular osteopontin (iOPN) and immunity, Immunol. Res. 49 (2011) 160–172.
[21] A. Baroni, A. De Filippis, E. Buommino, R.A. Satriano, V. Cozza, Osteopontin, a protein with cytokine-like properties: a possible involvement in pemphigus vulgaris, Arch. Dermatol. Res. 304 (2012) 237–240.
[22] Q. Tang, J.A. Bluestone, The Foxp3+ regulatory T cell: a jack of all trades, master of regulation, Nat. Immunol. 9 (2008) 239–244.
[23] Q. Tang, K.J. Henriksen, E.K. Boden, A.J. Tooley, J. Ye, S.K. Subudhi, X.X. Zheng, T.B. Strom, J.A. Bluestone, Cutting edge: CD28 controls peripheral homeostasis of CD4+CD25+ regulatory T cells, J. Immunol. 171 (2003) 3348–3352.
[24] M. Alecu, C. Ursaciuc, M. Surcel, G. Coman, D. Ciotaru, M. Dobre, CD28 T-cell costimulatory molecule expression in pemphigus vulgaris, J. Eur. Acad. Dermatol. Venereol. 23 (2009) 288–291.
[25] T. Schmidt, S. Willenborg, T. Hunig, C.A. Deeg, G. Sonderstrup, M. Hertl, R. Eming, Induction of T regulatory cells by the superagonistic anti-CD28 antibody D665 leads to decreased pathogenic IgG autoantibodies against desmoglein 3 in a HLA-transgenic mouse model of pemphigus vulgaris, Exp. Dermatol. 25 (2016) 293–298.
[26] M. Fujimoto, Regulatory B cells in skin and connective tissue diseases, J. Dermatol. Sci. 60 (2010) 1–7.
[27] C. Mauri, A. Bosma, Immune regulatory function of B cells, Annu. Rev. Immunol. 30 (2012) 221–241.
[28] H.Q. Zhu, R.C. Xu, Y.Y. Chen, H.J. Yuan, H. Cao, X.Q. Zhao, J. Zheng, Y. Wang, M. Pan, Impaired function of CD19(+) CD24(hi) CD38(hi) regulatory B cells in patients with pemphigus, Br. J. Dermatol. 172 (2015) 101–110.
[29] F. Giurdanella, L. Fania, M. Gnarra, P. Toto, D. Di Rollo, D.N. Sauder, C. Feliciani, A possible role for CD8+ T lymphocytes in the cell-mediated pathogenesis of pemphigus vulgaris, Mediators Inflamm. 2013 (2013) 764290.
[30] K. Boniface, J. Seneschal, M. Picardo, A. Taieb, Vitiligo: focus on clinical aspects, immunopathogenesis, and therapy, Clin. Rev. Allergy Immunol. 54 (2018) 52–67.
[31] S. Toosi, S.J. Orlow, P. Manga, Vitiligo-inducing phenols activate the unfolded protein response in melanocytes resulting in upregulation of IL6 and IL8, J. Invest. Dermatol. 132 (2012) 2601–2609.
[32] R. Yu, R. Broady, Y. Huang, Y. Wang, J. Yu, M. Gao, M. Levings, S. Wei, S. Zhang, A. Xu, M. Su, J. Dutz, X. Zhang, Y. Zhou, Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin, PLoS One 7 (2012) e51040.
[33] S. Itoi, A. Tanemura, Y. Kotobuki, M. Wataya-Kaneda, D. Tsuruta, M. Ishii, I. Katayama, Coexistence of Langerhans cells activation and immune cells infiltration in progressive nonsegmental vitiligo, J. Dermatol. Sci. 73 (2014) 83–85.
[34] C.Q. Wang, A.E. Cruz-Inigo, J. Fuentes-Duculan, D. Moussai, N. Gulati, M. Sullivan-Whalen, P. Gilleaudeau, J.A. Cohen, J.G. Krueger, Th17 cells and activated dendritic cells are increased in vitiligo lesions, PLoS One 6 (2011) e18907.
[35] J.M. Richmond, D.S. Bangari, K.I. Essien, S.D. Currimbhoy, J.R. Groom, A.G. Pandya, M.E. Youd, A.D. Luster, J.E. Harris, Keratinocyte-derived chemokines orchestrate T-Cell positioning in the Epidermis during vitiligo and may serve as biomarkers of disease, J. Invest. Dermatol. 137 (2017) 350–358.
[36] A.A. Abdellatif, A.M. Zaki, H.M. Abdo, D.G. Aly, T.A. Emara, S. El-Toukhy, H.M. Emam, M.S. Abdelwahab, Assessment of serum levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) among non-segmental vitiligo patients: a pilot study, Acta Dermatovenerol. Alp. Pannonica Adriat. 24 (2015) 43–45.
[37] A. Zloza, G.E. Lyons, L.K. Chlewicki, F.J. Kohlhapp, J.A. O'Sullivan, A.T. Lacek, T.V. Moore, M.C. Jagoda, V. Kumar, J.A. Guevara-Patino, Engagement of NK receptor NKG2D, but not 2B4, results in self-reactive CD8+ T cells and autoimmune vitiligo, Autoimmunity 44 (2011) 599–606.
[38] A. Bertolotti, K. Boniface, B. Vergier, D. Mossalayi, A. Taieb, K. Ezzedine, J. Seneschal, Type I interferon signature in the initiation of the immune response in vitiligo, Pigm. Cell Melanoma Res. 27 (2019) 398–407.
[39] J. Mosenson, A. Zloza, J. Klarquist, A.J. Barfuss, J.A. Guevara-Patino, I.C. Le Pool, HSP70i is a critical component of the immune response leading to vitiligo, Pigm. Cell Melanoma Res. 25 (2012) 88–98.
[40] L. Zhou, K. Li, Y.L. Shi, I. Hamzavi, T.W. Gao, M. Henderson, R.H. Huggins, O. Agbai, B. Mahmoud, X. Mi, H.W. Lim, Q.S. Mi, Systemic analyses of immunophenotypes of peripheral T cells in non-segmental vitiligo: implication of defective natural killer T cells, Pigm. Cell Melanoma Res. 25 (2012) 602–611.
[41] Y. Lili, W. Yi, Y. Ji, S. Yue, S. Weimin, L. Ming, Global activation of CD8+ cytotoxic T lymphocytes correlates with an impairment in regulatory T cells in patients with generalized vitiligo, PLoS One 7 (2012) e37513.
[42] R. Pichler, K. Sfetsos, B. Badics, S. Gutenbrunner, J. Berg, J. Auböck, Lymphocyte imbalance in vitiligo patients indicated by elevated CD4C/CD8C T-cell ratio, Wien. Med. Wochenschr. 159 (2009) 337–341.
[43] S. Li, G. Zhu, Y. Yang, Z. Jian, S. Guo, W. Dai, Q. Shi, R. Ge, J. Ma, L. Liu, K. Li, Q. Luan, G. Wang, T. Gao, C. Li, Oxidative stress drives CD8(+) T-cell skin trafficking in patients with vitiligo through CXCL16 upregulation by activating the unfolded protein response in keratinocytes, J. Allergy Clin. Immunol. 140 (2017) 177–189 e179.
[44] A. Rezk, D.M. Kemp, M. El-Domyati, W.H. El-Din, J.B. Lee, J. Uitto, O. Igoucheva, V. Alexeev, Misbalanced CXCL12 and CCL5 chemotactic signals in vitiligo onset and progression, J. Invest Dermatol. 137 (2017) 1126–1134.
[45] A. Rao, S. Gupta, A.K. Dinda, A. Sharma, V.K. Sharma, G. Kumar, D.K. Mitra, C.K. Prashant, G. Singh, Study of clinical, biochemical and immunological factors

determining stability of disease in patients with generalized vitiligo undergoing melanocyte transplantation, Br. J. Dermatol. 166 (2012) 1230–1236.
[46] F. Behfarjam, P. Mansouri, Z. Jadali, Imbalance of peripheral blood t helper type 17 responses in patients with vitiligo, Iran. J. Allergy Asthma Immunol. 17 (2018) 171–178.
[47] Zhou Li, Y.L. Shi, Kai Li, Iltefat Hamzavi, Tian-Wen Gao, Richard H. Huggins, Henry W. Lim, Qing-Sheng Mi, Increased circulating Th17 cells and elevated serumlevels of TGF-beta and IL-21 are correlated with humannon-segmental vitiligo development, Pigment Cell Melanoma Res. 28 (2015) 324–329.
[48] Y. Zhen, L. Yao, S. Zhong, Y. Song, Y. Cui, S. Li, Enhanced Th1 and Th17 responses in peripheral blood in active non-segmental vitiligo, Arch. Dermatol. Res. 308 (2016) 703–710.
[49] R. Khan, S. Gupta, A. Sharma, Circulatory levels of T-cell cytokines (interleukin [IL]-2, IL-4, IL-17, and transforming growth factor-beta) in patients with vitiligo, J. Am. Acad. Dermatol. 66 (2019) 510–511.
[50] F. Behfarjam, Z. Jadali, Vitiligo patients show significant up-regulation of aryl hydrocarbon receptor transcription factor, An. Bras. Dermatol. 93 (2018) 302–303.
[51] M. Tembhre, A.S. Parihar, V.K. Sharma, A. Sharma, P. Chattopadhyay, S. Gupta, Alteration in regulatory T cells and programmed death (PD)1 expressing regulatory T cells in active generalized vitiligo and their clinical correlation, Br. J. Dermatol. Syph. 172 (2015) 940–950.
[52] D.S. Hegab, M.A. Attia, Decreased circulating t regulatory cells in egyptian patients with nonsegmental vitiligo: correlation with disease activity, Dermatol. Res. Pract. 2015 (2015) 145409.
[53] M.K. Tembhre, V.K. Sharma, A. Sharma, P. Chattopadhyay, S. Gupta, T helper and regulatory T cell cytokine profile in active, stable and narrow band ultraviolet B treated generalized vitiligo, Clin. Chim. Acta 424 (2013) 27–32.
[54] M.K. Tembhre, A.S. Parihar, A. Sharma, S. Gupta, P. Chattopadhyay, V.K. Sharma, Participation of T cell immunoglobulin and mucin domain-3 (TIM-3) and its ligand (galectin-9) in the pathogenesis of active generalized vitiligo, Immunol. Res. 62 (2015) 23–34.
[55] X. Miao, R. Xu, B. Fan, J. Chen, X. Li, W. Mao, S. Hua, B. Li, PD-L1 reverses depigmentation in Pmel-1 vitiligo mice by increasing the abundance of Tregs in the skin, Sci. Rep. 8 (2018) 1–6.
[56] A. Batycka-Baran, J. Maj, R. Wolf, J.C. Szepietowski, The new insight into the role of antimicrobial proteins-alarmins in the immunopathogenesis of psoriasis, J. Immunol. Res. 2014 (2014) 628289.
[57] S. Morizane, R.L. Gallo, Antimicrobial peptides in the pathogenesis of psoriasis, J. Dermatol. 39 (2012) 225–230.
[58] A. Batycka-Baran, E. Hattinger, S. Zwicker, B. Summer, O.M. Zack Howard, P. Thomas, J.C. Szepietowski, T. Ruzicka, J.C. Prinz, R. Wolf, Leukocyte-derived koebnerisin (S100A15) and psoriasin (S100A7) are systemic mediators of inflammation in psoriasis, J. Dermatol. Sci. 79 (2015) 214–221.
[59] S.T. Oh, A. Schramme, W. Tilgen, P. Gutwein, J. Reichrath, Overexpression of CXCL16 in lesional psoriatic skin, Dermatoendocrinology 1 (2009) 114–118.
[60] S. Steffen, S. Abraham, M. Herbig, F. Schmidt, K. Blau, S. Meisterfeld, S. Beissert, J. Guck, C. Gunther, Toll-like receptor-mediated upregulation of CXCL16 in psoriasis orchestrates neutrophil activation, J. Invest. Dermatol. 138 (2018) 344–354.
[61] S.Y. Hu, Yen H, Lin F, Chen C, Lan G, CE, Neutrophil extracellular trap formation is increased in psoriasis and induces human β-defensin-2 production in epidermal keratinocytes, Sci. Rep. 6 (2016).
[62] A. Lin, C.J. Rubin, R. Khandpur, J.Y. Wang, M.B. Riblett, S. Yalavarthi, E.C. Villanueva, P. Shah, M.J. Kaplan, A.T. Bruce, Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis, J. Immunol. 187 (2011) 490–500.
[63] M. Kakeda, C. Schlapbach, G. Danelon, M.M. Tang, V. Cecchinato, N. Yawalkar, M. Uguccioni, Innate immune cells express IL-17A/F in acute generalized exanthematous pustulosis and generalized pustular psoriasis, Arch. Dermatol. Res. 306 (2014) 933–938.
[64] S. Glatt, D. Baeten, T. Baker, M. Griffiths, L. Ionescu, A.D.G. Lawson, A. Maroof, R. Oliver, S. Popa, F. Strimenopoulou, P. Vajjah, M. Watling, N. Yeremenko, P. Miossec, S. Shaw, Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation, Ann. Rheum. Dis. 77 (2018) 523–532.
[65] R. Leite Dantas, D. Masemann, T. Schied, V. Bergmeier, T. Vogl, K. Loser, B. Brachvogel, G. Varga, S. Ludwig, V. Wixler, Macrophage-mediated psoriasis can be suppressed by regulatory T lymphocytes, J. Pathol. 240 (2016) 366–377.
[66] J. Fuentes-Duculan, M. Suarez-Farinas, L.C. Zaba, K.E. Nograles, K.C. Pierson, H. Mitsui, C.A. Pensabene, J. Kzhyshkowska, J.G. Krueger, M.A. Lowes, A subpopulation of CD163-positive macrophages is classically activated in psoriasis, J. Invest. Dermatol. 130 (2010) 2412–2422.
[67] N. Yawalkar, G.G. Tscharner, R.E. Hunger, A.S. Hassan, Increased expression of IL-12p70 and IL-23 by multiple dendritic cell and macrophage subsets in plaque psoriasis, J. Dermatol. Sci. 54 (2009) 99–105.
[68] C.T.H. Nguyen, N. Kambe, F. Yamazaki, I. Ueda-Hayakawa, I. Kishimoto, H. Okamoto, Up-regulated expression of CD86 on circulating intermediate monocytes correlated with disease severity in psoriasis, J. Dermatol. Sci. 90 (2018) 135–143.
[69] D. Ilkovitch, L.K. Ferris, Myeloid-derived suppressor cells are elevated in patients with psoriasis and produce various molecules, Mol. Med. Rep. 14 (2016) 3935–3940.
[70] D.C. Soler, A.B. Young, L. Fiessinger, F. Galimberti, S. Debanne, S. Groft, T.S. McCormick, K.D. Cooper, Increased, but functionally impaired, CD14(+) HLA-DR(-/low) myeloid-derived suppressor cells in psoriasis: a mechanism of dysregulated t cells, J. Invest. Dermatol. 136 (2016) 798–808.
[71] J. Skrzeczynska-Moncznik, K. Wawro, A. Stefanska, E. Oleszycka, P. Kulig, B.A. Zabel, M. Sulkowski, M. Kapinska-Mrowiecka, M. Czubak-Macugowska, E.C. Butcher, J. Cichy, Potential role of chemerin in recruitment of plasmacytoid dendritic cells to diseased skin, Biochem. Biophys. Res. Commun. 380 (2009) 323–327.
[72] L.C. Zaba, J. Fuentes-Duculan, N.J. Eungdamrong, M.V. Abello, I. Novitskaya, K.C. Pierson, J. Gonzalez, J.G. Krueger, M.A. Lowes, Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells, J. Invest. Dermatol. 129 (2009) 79–88.
[73] H. Fujita, A. Shemer, M. Suarez-Farinas, L.M. Johnson-Huang, S. Tintle, I. Cardinale, J. Fuentes-Duculan, I. Novitskaya, J.A. Carucci, J.G. Krueger, E. Guttman-Yassky, Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets, J. Allergy Clin. Immunol. 128 (2011) 574–582 e571-512.
[74] S.E. Dunphy, C.M. Sweeney, G. Kelly, A.M. Tobin, B. Kirby, C.M. Gardiner, Natural killer cells from psoriasis vulgaris patients have reduced levels of cytotoxicity associated degranulation and cytokine production, Clin. Immunol. 177 (2015) 43–49.
[75] U. Laggner, P. Di Meglio, G.K. Perera, C. Hundhausen, K.E. Lacy, N. Ali, C.H. Smith, A.C. Hayday, B.J. Nickoloff, F.O. Nestle, Identification of a novel proinflammatory human skin-homing Vgamma9Vdelta2 T cell subset with a potential role in psoriasis, J. Immunol. 187 (2011) 2783–2793.
[76] R. Yoshiki, K. Kabashima, T. Honda, S. Nakamizo, Y. Sawada, K. Sugita, H. Yoshioka, S. Ohmori, B. Malissen, Y. Tokura, M. Nakamura, IL-23 from Langerhans cells is required for the development of imiquimod-induced psoriasis-like dermatitis by induction of IL-17A-producing gammadelta T cells, J. Invest. Dermatol. 134 (2014) 1912–1921.
[77] N.L. Ward, D.T. Umetsu, A new player on the psoriasis block: IL-17A- and IL-22-producing innate lymphoid cells, J. Invest. Dermatol. 134 (2014) 2305–2307.
[78] V.R. Khairutdinov, A.F. Mikhailichenko, I.E. Belousova, E.S. Kuligina, A.V. Samtsov, E.N. Imyanitov, The role of intradermal proliferation of T-cells in the pathogenesis of psoriasis, An. Bras. Dermatol. 92 (2017) 41–44.
[79] C. Johansen, A.H. Rittig, M. Mose, T. Bertelsen, I. Weimar, J. Nielsen, T. Andersen, T.K. Rasmussen, B. Deleuran, L. Iversen, STAT2 is involved in the pathogenesis of psoriasis by promoting CXCL11 and CCL5 production by keratinocytes, PLoS One 12 (2017) e0176994.
[80] H. Mitsui, M. Suarez-Farinas, D.A. Belkin, N. Levenkova, J. Fuentes-Duculan, I. Coats, H. Fujita, J.G. Krueger, Combined use of laser capture microdissection and cDNA microarray analysis identifies locally expressed disease-related genes in focal regions of psoriasis vulgaris skin lesions, J. Invest. Dermatol. 132 (2012) 1615–1626.
[81] M. Priyadarssini, D. Divya Priya, S. Indhumathi, M. Rajappa, L. Chandrashekar, D.M. Thappa, Immunophenotyping of T cells in the peripheral circulation in psoriasis, Br. J. Biomed. Sci. 73 (2016) 174–179.
[82] S. Jain, I.R. Kaur, S. Das, S.N. Bhattacharya, A. Singh, T helper 1 to T helper 2 shift in cytokine expression: an autoregulatory process in superantigen-associated psoriasis progression? J. Med. Microbiol. 58 (2009) 180–184.
[83] S.G.V. Khandpur, D. Das, A. Sharma, Is there a correlation of serum and tissue T helper-1 and -2 cytokine profiles with psoriasis activity and severity? A cross-sectional study, Indian J. Dermatol. Venereol. Leprol. 84 (2018) 414–418.
[84] K. Zhu, J. Ye, M. Wu, H. Cheng, Expression of Th1 and Th2 cytokine-associated transcription factors, T-bet and GATA-3, in peripheral blood mononuclear cells and skin lesions of patients with psoriasis vulgaris, Arch. Dermatol. Res. 302 (2010) 517–523.
[85] E. Buommino, M.A. Tufano, N. Balato, N. Canozo, M. Donnarumma, L. Gallo, A. Balato, F. Ayala, Osteopontin: a new emerging role in psoriasis, Arch. Dermatol. Res. 301 (2009) 397–404.
[86] M. Mansouri, P. Mansouri, A.A. Raze, Z. Jadali, The potential role of Th17 lymphocytes in patients with psoriasis, An. Bras. Dermatol. 93 (2018) 63–66.
[87] L.-L.W. Ying Wang, Hao-Yu Yang, Fei-Fei Wang, Xue-Xiu Zhang, Yan-Ping Bai, Interleukin-21 is associated with the severity of psoriasis vulgaris through promoting CD4+ T cells to differentiate into Th17 cells, Am. J. Transl. Res. 8 (2016) 3188–3196.
[88] L. Ma, H. Xue, T. Gao, M. Gao, Y. Zhang, Notch1 signaling regulates the Th17/Treg immune imbalance in patients with psoriasis vulgaris, Mediators Inflamm. (2018) 1–10.
[89] A. Arakawa, S. Vollmer, P. Besgen, A. Galinski, B. Summer, Y. Kawakami, A. Wollenberg, K. Dornmair, M. Spannagl, T. Ruzicka, T. Thomas, J.C. Prinz, Unopposed IL-36 activity promotes clonal CD4+ T-cell responses with IL-17A production in generalized pustular psoriasis, J. Invest. Dermatol. 138 (2018) 1338–1347.
[90] W. Chen, Y. Gong, X. Zhang, Y. Tong, X. Wang, C. Fei, H. Xu, Q. Yu, Y. Wang, Y. Shi, Decreased expression of IL-27 in moderate-to-severe psoriasis and its anti-inflammation role in imiquimod-induced psoriasis-like mouse model, J. Dermatol. Sci. 85 (2017) 115–123.
[91] P. Varshney, N. Saini, PI3K/AKT/mTOR activation and autophagy inhibition plays a key role in increased cholesterol during IL-17A mediated inflammatory response in psoriasis, Biochim. Biophys. Acta Mol. Basis Dis. 1864 (2016) 1795–1803.
[92] E. Witte, G. Kokolakis, K. Witte, S. Philipp, W. Doecke, N. Babel, B.M. Wittig, K. Warszawska, A. Kurek, M. Erdmann-Keding, S. Kunz, K. Asadullah, M.E. Kadin, H.D. Volk, W. Sterry, K. Wolk, R. Saba, IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis, J. Invest. Dermatol. 134 (2014) 2757–2767.
[93] H.L. Ha, H. Wang, P. Pisitkun, J.C. Kim, I. Tassi, W. Tang, M.I. Morasso, M.C. Udey, U. Siebenlist, IL-17 drives psoriatic inflammation via distinct, target

cell-specific mechanisms, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E3422–3431.
[94] K.E. Nograles, L.C. Zaba, E. Guttman-Yassky, J. Fuentes-Duculan, M. Suarez-Farinas, I. Cardinale, A. Khatcherian, J. Gonzalez, K.C. Pierson, T.R. White, C. Pensabene, I. Coats, I. Novitskaya, M.A. Lowes, J.G. Krueger, Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways, Br. J. Dermatol. 159 (2008) 1092–1102.
[95] C. Schlapbach, A. Gehad, C. Yang, R. Watanabe, E. Guenova, J.E. Teague, L. Campbell, N. Yawalkar, T.S. Kupper, R.A. Clark, Human TH9 cells are skin-tropic and have autocrine and paracrine proinflammatory capacity, Sci. Transl. Med. 6 (2014) 219ra218.
[96] Y. Wang, L. Wang, H. Yang, W. Yuan, J. Ren, Y. Bai, Activated circulating t follicular helper cells are associated with disease severity in patients with psoriasis, J. Immunol. Res. 2016 (2016) 7346030.
[97] D. Shin, D.S. Kim, S.H. Kim, J.H. Je, H.J. Kim, D. Young Kim, S.M. Kim, M.G. Lee, Decreased PD-1 positive blood follicular helper T cells in patients with psoriasis, Arch. Dermatol. Res. 308 (2016) 593–599.
[98] W.A. Goodman, A.D. Levine, J.V. Massari, H. Sugiyama, T.S. McCormick, K.D. Cooper, IL-6 signaling in psoriasis prevents immune suppression by regulatory T cells, J. Immunol. 183 (2009) 3170–3176.
[99] L. Yang, B. Li, E. Dang, L. Jin, X. Fan, G. Wang, Impaired function of regulatory T cells in patients with psoriasis is mediated by phosphorylation of STAT3, J. Dermatol. Sci. 81 (2015) 85–92.
[100] D. Brandt, M. Sergon, S. Abraham, K. Mabert, C.M. Hedrich, TCR (+)CD3(+)CD4(-)CD8(-) effector T cells in psoriasis, Clin. Immunol. 181 (2017) 51–59.
[101] J. Kim, R. Bissonnette, J. Lee, J. Correa da Rosa, M. Suarez-Farinas, M.A. Lowes, J.G. Krueger, The Spectrum of mild to severe psoriasis vulgaris is defined by a common activation of IL-17 pathway genes, but with key differences in immune regulatory genes, J. Invest. Dermatol. 136 (2016) 2173–2182.
[102] J. Bartosinska, J. Purkot, M. Kowal, A. Michalak-Stoma, D. Krasowska, G. Chodorowska, K. Giannopoulos, The expression of selected molecular markers of immune tolerance in psoriatic patients, Adv. Clin. Exp. Med. 27 (2018) 721–725.
[103] H. Wu, W. Liao, Q. Li, H. Long, H. Yin, M. Zhao, V. Chan, C.S. Lau, Q. Lu, Pathogenic role of tissue-resident memory T cells in autoimmune diseases, Autoimmun. Rev. 17 (2018) 906–911.
[104] K. Boniface, C. Jacquemin, A.S. Darrigade, B. Dessarthe, C. Martins, N. Boukhedouni, C. Vernisse, A. Grasseau, D. Thiolat, J. Rambert, F. Lucchese, A. Bertolotti, K. Ezzedine, A. Taieb, J. Seneschal, Vitiligo skin is imprinted with resident memory CD8 t cells expressing CXCR3, J. Invest. Dermatol. 138 (2018) 355–364.
[105] S. Cheuk, M. Wiken, L. Blomqvist, S. Nylen, T. Talme, M. Stahle, L. Eidsmo, Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis, J. Immunol. 192 (2014) 3111–3120.
[106] T. Hartwig, S. Pantelyushin, A.L. Croxford, P. Kulig, B. Becher, Dermal IL-17-producing gammadelta T cells establish long-lived memory in the skin, Eur. J. Immunol. 45 (2015) 3022–3033.

Dayasagar Das has graduated his Master in Science in Microbiology from Kasturba Medical College, Manipal University, India. He is currently a PhD student at Dr. Alpana Sharma's Lab at Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), New Delhi, India. His doctoral thesis is focused on "exploring the plasticity of gamma delta T cell in autoimmune blistering skin disease, Pemphigus vulgaris". He has received GP Talwar Young Scientist award during his PhD. He has also availed many International Travel grants to attend the conferences.

Dr. Shamima Akhtar has graduated her PhD from Institute of Molecular Cardiovascular Research (IMCAR, University Hospital), Aachen, Germany. She received DAAD-Siemens scholarship to persue her PhD from 2009-2013. Her PhD research focused on stabilizing atherosclerotic plaques by CXCL12 treatment and studying the role of HIF-1α in atherosclerosis. Presently, she is a post-doctoral fellow in Dr. Alpana Sharma's Lab at Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), New Delhi, India. She received competitive National Post-Doctoral Fellowship from Department of Science and Technology (DST) India for her current position. Her post-doctoral work focuses on stratifying different stages of endothelial dysfunction and validating them in cardiovascular patients.

Santosh Kurra has obtained his Master in Science from GITAM University, India. Presently, is a PhD Student at Dr. Alpana Sharma's Lab at Department of Biochemistry, AIIMS, New Delhi, India. The focus of his PhD is studying the role of gamma delta T cells in the pathogenesis of Vitiligo.

Dr. Somesh Gupta, is a professor and practicing clinician at Department of Dermatology and Venerology at All India Institute of Medical Sciences (AIIMS), New Delhi, India. He obtained his MD in Dermatology and Venerology from Government Medical College, Jabalpur, MP, India in 1997. His main focus of research is on Vitiligo and Psoriasis. He is the recipient of many national awards such as, Dermatology Excellence Award (2003–2004) Vishnu Priya Devi IADVL Award Appreciation Award by IADVL Dr. P.S. Ranganathan Memorial Award Dr. V. Govindan Nair Memorial Prize To date, he has authored more than 200 peer-reviewed papers.

Dr. Alpana Sharma is a professor at Department of Biochemistry, AIIMS, New Delhi, India. She received her PhD and MPhil in Biochemistry from JN Medical College, Aligarh Muslim University, India. Her broad area of research interest includes immunopathogenesis of autoimmune skin diseases such as pemphigus, vitiligo and psoriasis. She is a recipient of many national and international awards e.g. Indo-French Fellowship, and ACR-NCI International Investigator award (USA), AIIMS Excellence Research Award etc. She is member of National Academy of Medical Sciences, National Academy of Sciences, and Indian Immunological Society. She is Treasurer of Indian Immunology Society. She is guiding many pH.D., M.D. and M.Sc. students for their dissertation. Her research work is funded by various national funding agencies such as Department of Biotechnology (DBT), Indian Council of Medical Research (ICMR), Council of Scientific and Industrial Research (CSIR), etc. She has written two books, contributed 23 chapters in various textbooks and published more than 110 research articles in peer-reviewed Journals.