

REVIEW

New insights of T cells in the pathogenesis of psoriasis

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Psoriasis is one of the most common immune-mediated chronic, inflammatory skin diseases characterized by hyperproliferative keratinocytes and infiltration of T cells, dendritic cells, macrophages and neutrophils. Although the pathogenesis of psoriasis is not fully understood, there is ample evidence suggesting that the dysregulation of immune cells in the skin, particularly T cells, plays a critical role in psoriasis development. In this review, we mainly focus on the pathogenic T cells and discuss how these T cells are activated and involved in the disease pathogenesis. Newly identified 'professional' IL-17-producing dermal $\gamma\delta$ T cells and their potential role in psoriasis will also be included. Finally, we will briefly summarize the recent progress on the T cell and its related cytokine-targeted therapy for psoriasis treatment.

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INTRODUCTION

Psoriasis is a common, chronic inflammatory skin disease, affecting about 2% of the worldwide population.¹ Psoriasis vulgaris is the most common type of psoriasis, manifested as dry, red raised plaques with adherent silvery scales. Histologically, psoriasis is characterized by hyperproliferation and aberrant differentiation of keratinocytes, dilated, hyperplastic blood vessels as well as an inflammatory infiltration of leukocytes, predominantly into the dermis.² Until the late 1970s, psoriasis was originally thought to be a disease primarily of dysfunctional epidermal keratinocytes.³ However, substantial clinical and basic research observations indicate that the cellular innate and adaptive immune responses, especially the activation of T cells, play a critical role in the pathogenesis of psoriasis. The successful treatment of psoriasis patients with cyclosporine A, an immunosuppressive agent that inhibits T-cell proliferation and cytokine production, was the first clinical evidence to suggest a potential role of T cells in psoriasis pathogenesis.⁴ Other T cell-targeted drugs such as anti-CD4 monoclonal antibody and cytotoxic T lymphocyte-associated antigen 4-immunoglobulin were also observed to have a significant therapeutic efficacy in psoriasis treatment.^{5–7} In addition, an earlier *in vitro* study showing that activated CD4⁺ T cells from psoriatic lesions could enhance keratinocyte proliferation *via* secretion of interferon- γ (IFN- γ)⁸ and the establishment of psoriasis xenograft animal model in severe combined immunodeficient mouse^{9,10} further confirm the importance of T cells in psoriasis development. Thus, psoriasis is considered to be an organ-specific T cell-driven inflammatory disease and T cells play a dominant pathogenic role in the initiation and maintenance of psoriasis. In the past few years, many new findings on T cells and their contributions to the disease development have challenged our conventional views regarding psoriasis as a T helper

(Th) 1-mediated skin disease and prompted us to reassess T-cell functions in psoriasis. In this review, we will summarize recent progress on T cells as well as some important innate immune cells and their roles in the pathogenesis of psoriasis. Finally, we will briefly discuss some newly developed biological agents targeting T cells and the related cytokines, and their therapeutic efficacy in the treatment of psoriasis patients.

WHAT CAUSES THE ACTIVATION OF PATHOGENIC T CELLS IN PSORIASIS?

As a T cell-mediated autoimmune skin disease, an important question in psoriasis that attracts researchers' interest is to understand how the pathogenic T cells become activated during disease development. The close relationship between streptococcal infection and psoriasis have made antigen(s) from streptococcus the main candidate responsible for activating T cells.^{11,12} The concept of superantigen was initially proposed based on several research findings where psoriasis patients had a restricted T-cell receptor (TCR) V β usage in the peripheral blood and lesions.^{13,14} Additionally, streptococcal exotoxins could induce expression of a skin-homing receptor, cutaneous lymphocyte-associated antigen, on T cells.¹⁵ However, an oligoclonal T-cell expansion found in psoriasis lesions has been reported by several independent groups when analyzing TCR usage on the infiltrated T cells, which provides clear evidence in favor of an antigen-specific T-cell response in the local lesion.^{16,17} Furthermore, the identification of conserved clonal TCR rearrangement within skin lesions from different patients and continuous presence of the same T-cell clone over a prolonged period of time, even in relapsing disease, suggest that the T cells, which mediate chronic psoriasis, are driven by common antigen(s).^{18,19} These findings along with the fact that streptococcal M

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protein shares a high similar structure with type I keratins propose a new theory in psoriasis, named molecular mimicry, or disease mimicry. The concept of molecular mimicry explains how anti-streptococcal T cells can be activated in the skin to target-specific tissue antigen(s) and subsequently causing disease.^{20,21} Indeed, peripheral blood T cells from psoriatic patients but not healthy controls have been shown to respond to several synthetic peptides corresponding to these shared homologous sequence motifs for the production of IFN- γ .^{22,23} Further study demonstrated that CD8⁺ T cells in the peripheral blood from psoriasis patients carrying the HLA-Cw6 allele, which has been reported to have a strong association with psoriasis, had a significant IFN- γ response to the peptide selected from the shared sequence by keratin 17 and M6 protein and the predicted HLA-Cw6 binding.²⁴ Additionally, the majority (>90%) of these responding cells express the skin homing cutaneous lymphocyte-associated antigen determinant.²⁴ Autoantigen candidates Ezrin, Maspin, Peroxiredoxin 2 and Heat Shock Protein 27, all of which have homologies to streptococcal proteins, have been shown to react with the sera from psoriasis patients.²⁵

However, several studies from Fry's group suggested that streptococcal M protein might not be the target for the lesional skin T cells.^{26,27} In these studies, T-cell lines grown from lesional dermis did not respond by proliferation to recombinant M protein.²⁸ Alternatively, they found that at least half of the streptococcal cell wall-specific Th1 cells in psoriasis lesions were specific for streptococcal peptidoglycan (PG), a major component of the Gram-positive bacterial cell wall.²⁹ In dermal lesions, there were observations of increased numbers of macrophages, containing streptococcal PG, within clusters of dermal T cells or in the dermal papillae.²⁹ It is well known that PG is a strong pro-inflammatory stimulus in chronic inflammation through its interaction with dendritic cells (DCs) and monocytes *via* pattern recognition receptors including Toll-like receptor 2, nucleotide-binding oligomerization domains 1 and 2 and PG recognition proteins 1–4.^{30,31} Interestingly, the genes encoding the above PG recognition receptors are all located within linkage sites associated with psoriasis.³² On the basis of these findings, the authors proposed that PG is a major etiological factor in psoriasis and an altered innate response to PG might contribute to the enhanced pathogenic T-cell activation and expansion in the psoriasis lesion.³³ However, this schema does not well address the role of CD8⁺ T-cell function in psoriasis, which has been found to be essential for the development of psoriatic lesions.³⁴ Thus, Valdimarsson *et al.*³⁵ recently proposed a modified schematic model to explain the potential role of CD4⁺ and CD8⁺ T cells in the development of psoriasis lesions and how streptococcal infection triggers and maintains psoriasis. In addition to the streptococcal PG, we also found that streptococcal CpG DNA could enhance the proliferation and activation of peripheral T cells from psoriasis patients upon stimulated with streptococcal antigen, indicating that integral function of streptococcal antigen, particularly streptococcal DNA, in the pathogenesis of psoriasis.³⁶ Thus far, the (auto)antigen(s) responsible for activating psoriatic T cells is still controversial and remains to be determined. Future studies should focus on identifying the autoantigen triggering psoriatic T cells, as it could lead to the use of a vaccine therapy for the treatment of psoriasis.

IS PSORIASIS A TH1 AND/OR TH17 CELL-MEDIATED INFLAMMATORY SKIN DISEASE?

For over 30 years, T cells were classified as Th1 or Th2 cells by production of defining cytokines, IFN- γ and interleukin (IL)-4, respectively. In psoriatic plaques and peripheral blood of psoriatic patients,

there were large numbers of CD4⁺ Th1 and CD8⁺ cytotoxic T cells type 1 (Tc1) cells as well as elevated cytokine levels of IFN- γ , tumor-necrosis factor (TNF)- α and IL-12, which well defined psoriasis as a Th1 cell-mediated disease.^{37–39} Since then, it has been widely recognized that the interaction of T cells and DCs creates a 'type 1' inflammatory environment by secreting large amounts of Th1 type cytokines, leading to the development of psoriasis.⁴⁰

Recently, a new population of IL-17-producing CD4⁺ Th cells, named Th17, has been identified and shown to be involved in the models of inflammatory and autoimmune diseases.^{41–43} It has been well documented that IL-23 functions as a key cytokine for the maintenance and development of both murine and human Th17 cells.^{44–47} IL-23 is a heterodimeric cytokine that has unique subunit IL-23p19 combined with IL-12p40, shared with IL-12.⁴⁸ There is growing evidence to suggest that Th17 cells and their related cytokines such as IL-17A, IL-17F, IL-22, IL-21 and IL-26 play essential roles in a variety of chronic inflammatory diseases, including psoriasis. Th17 cells and their downstream effector molecules, which include IL-17A, IL-17F, IL-22, IL-21 and TNF- α , are found at increased levels in psoriatic skin and circulation.^{49–52} Moreover, psoriatic skin lesions also contain high mRNA and protein levels of IL-23 compared with non-lesional and normal skin and IL-23 has been found to be produced mainly by the activated macrophages and DCs.^{53–55} Intradermal injection of IL-23 or IL-21 in mice can stimulate keratinocytes proliferation and cause epidermal hyperplasia (acanthosis), which is one of the most significant features in human psoriasis.^{51,56} Further studies demonstrated that IL-22, IL-17A as well as CC chemokine receptor (CCR) 6 are all required for IL-23-induced psoriasis-like skin inflammation.^{57–59} In addition, IL-22 was also shown to be critical in another murine psoriasisform model triggered by topical application of Toll-like receptor 7/8 agonist Imiquimod.⁶⁰ More importantly, these released Th17-related cytokines can further act on keratinocytes and other inflammatory cells infiltrated in the skin, thus amplifying the local inflammation as well as causing keratinocyte hyperproliferation. It has been reported that IL-17A can upregulate keratin 17 expression on keratinocytes, which was regarded as a hallmark of psoriasis.⁶¹ Meanwhile, IL-17A plus IL-22 can synergistically enhance keratinocyte expression of antimicrobial peptides, although each cytokine modulates distinct inflammatory and keratinocyte-response pathways that compensatively contribute to the psoriatic phenotype.^{62–64}

Collectively, these studies indicate the important role of IL-23/Th17 axis in psoriasis development, which challenges the definition of psoriasis to be a Th1 cell-mediated disease. Th1 and Th17 cells are known as distinct polarized Th cell types, but they are often colocalized in pathological environments, as both Th1 and Th17 cells are increased in the psoriatic lesions and peripheral blood.^{50,52} To address these questions, Kryczek *et al.*⁶⁵ found that IFN- γ is a potent promoter of human IL-17⁺ T-cell trafficking, induction and function. IFN- γ synergized with IL-17 could enhance human normal keratinocyte to produce human β -defensin 2, suggesting that Th1 and Th17 cells may collaboratively interact with each other and contribute to the autoimmune disease pathogenesis.⁶⁵ This concept is well supported by another study, in which the authors found that there was accumulation of Th1/Th17 cell-polarizing myeloid DCs in the psoriatic lesions.⁶⁶ Additionally, intradermal injection of IFN- γ into the non-lesional skin of psoriasis patients could induce significant infiltration of T cells and inflammatory DCs as well as the production of chemokines and cytokines, including IL-23.⁶⁷

Recently, another distinct population of Th cells, which preferentially express CCR10, CCR6 and CCR4 and produce only IL-22, but

not IL-17 or IFN- γ , has been characterized and called IL-22-producing Th cells (Th22).^{68,69} This unique subset of human skin-homing memory T cells may be involved in epidermal immunity and remodeling and dedicated to the skin homeostasis and pathology.⁷⁰ It has been reported that there were more Th22 cells along with Th1 and Th17 cells in the circulation of psoriatic patients.⁵² Res *et al.*⁷¹ also demonstrated that there were more IL-22-producing CD8⁺ T cells (Tc22) along with Tc17 (IL-17-producing CD8⁺ T cells) in the psoriatic lesions. They found these Th22 and Tc22 cells might arise from IL-17-producing cells (Th17 and Tc17 cells), suggesting these cells acquire plastic ability in their development. Therefore, psoriasis cannot be simply defined as one subset of Th cells-mediated disease. Instead, all these pathogenic Th cells are implicated in the disease development, which interact with other types of T cells, DCs and neutrophils to create a chronic inflammatory environment for the maintenance of psoriatic plaque.

INNATE IMMUNE T CELLS OR INNATE EFFECTOR CELLS IN PSORIASIS PATHOGENESIS

In addition to these conventional T cells, more attention has been drawn recently on the innate immune cells, such as gamma delta ($\gamma\delta$) T cells, natural killer (NK) cells and natural killer T (NKT) cells and their potential roles in psoriasis.

Murine skin contains abundant $\gamma\delta$ T cells in the epidermis, called dendritic epidermal $\gamma\delta$ T cells.^{72,73} The development and function of dendritic epidermal $\gamma\delta$ T cells have been well defined for decades.^{74–76} Recently, three laboratories including ours have identified a novel $\gamma\delta$ T-cell subset in the dermis.^{55,77,78} Unlike dendritic epidermal $\gamma\delta$ T cells and conventional $\alpha\beta$ T cells, dermal $\gamma\delta$ T cells constitutively express IL-23 receptor, CCR6 and transcriptional factor ROR γ t. More importantly, these cells are demonstrated to be the major IL-17 producer in the skin upon IL-23 stimulation. It has been demonstrated that $\gamma\delta$ T cells from other anatomical sites have important pathogenic roles in some infectious and autoimmune diseases through their ability to rapidly produce IL-17 upon IL-23 and IL-1 β or danger signal stimulation even in the absence of TCR ligation.^{79–81} Thus, $\gamma\delta$ T cells are considered as innate-like cells and can amplify the conventional acquired immune response. Not surprisingly, as ‘professional’ IL-17-producing cells, dermal $\gamma\delta$ T cells are also found very critical in the psoriasis pathogenesis.⁵⁵ In TCR δ -deficient (*TCR δ ^{-/-}*) mice, the epidermal hyperplasia and inflammation induced by IL-23 and Imiquimod were significantly decreased. Consistent with our finding, Mabuchi *et al.*⁸² also showed IL-23 induced less severe skin pathology in *TCR δ ^{-/-}* mice, but they claimed there were specific epidermal CCR6 positive $\gamma\delta$ T cells which were responsible in this murine skin inflammation model. The discrepancy between their findings and ours could be explained by the possibility that dermal $\gamma\delta$ T cells might migrate into the epidermis during the inflammation. This notion is supported by the finding that this subset of $\gamma\delta$ T cells is scarce in epidermis under a steady condition.⁵⁵ We also found that dermal $\gamma\delta$ T cells expanded upon IL-23 stimulation. Importantly, high frequency of $\gamma\delta$ T cells was found in the lesions of psoriatic patients, which closely link the murine model system to the clinics. These $\gamma\delta$ T cells in the human skin were also capable of producing large amounts of IL-17 upon IL-23 stimulation as the murine counterpart did. Recently, Nestle’s group also reported a novel skin homing V γ 9V δ 2 T-cell subset in humans, which expressed cutaneous lymphocyte-associated antigen and other skin homing chemokine receptors. In psoriasis patients, this population was found to be significantly decreased in the peripheral blood, but increased in the lesion.⁸³ Taken together, we assume

these $\gamma\delta$ T cells present in the skin may become the first line of defense against the invasion of foreign pathogens or the danger signals released upon infection. The released cytokines after $\gamma\delta$ T-cell activation can further trigger the downstream immune response, thus causing the chronic inflammation in the local skin. Thus far, the function of dermal $\gamma\delta$ T cells, especially in humans, is not fully understood and need to be further investigated in the future.

Additional innate immune cells involved in psoriasis are NK and NKT cells. NKT cells are a heterogenous subset of T cells that share features of both T cells and NK cells. Activated NKT cells can induce psoriasis in xenograft mouse model by using non-lesional psoriatic skin.^{84,85} Both NK and NKT cells infiltrations have been found significantly increased in psoriatic lesions.^{86,87} Infiltrating NK cells express CXCR3, CCR5 and CCR6 as well, which are in response to the corresponding chemokines CXCL10, CCL5 or CCL20 secreted by keratinocytes. Additionally, psoriatic NK cells might have increased cytotoxicity through the release of cytotoxic granules such as perforin, which were found upregulated in the psoriatic lesions.⁸⁷ Recently, NKT cells have been demonstrated to be a potent IL-17 producer, suggesting that these cells may act similarly as dermal $\gamma\delta$ T cells in psoriasis pathogenesis.⁸⁸

In addition to these unconventional T cells, Lin *et al.*⁸⁹ reported that mast cells and neutrophils were prominent cells that produced IL-17 in the skin of healthy controls as well as psoriasis patients. In addition, it has been shown that there is a specific IL-23-responsive innate lymphoid population in the intestine, which mediates intestinal immunopathology in inflammatory bowel disease.⁹⁰ It is possible there might be a similar cell population in psoriatic lesions.

REGULATORY T CELLS (TREGS)

Tregs are a subset of T lymphocytes that suppress not only auto-immune responses but also other aberrant or excessive immune responses to non-self-antigens.⁹¹ Although similar proportions of Tregs have been found in normal and psoriatic peripheral blood, both *in vitro* and *in vivo* experiments have suggested that Tregs did not function properly in psoriatic plaques. Psoriatic Tregs, in which cells were isolated from lesional psoriatic skin or sorted from peripheral blood of psoriatic patients, are functionally deficient in suppressing effector T-cell responses in either alloantigen-specific or polyclonal TCR stimulation assays.⁹² Furthermore, in a psoriasis mouse model which was established by knocking out CD18, the primary dysfunction of Tregs has been found to allow subsequent hyperproliferation of pathogenic T cells.⁹³ The possible mechanism by which Tregs exhibit decreased suppression function is partially due to the pro-inflammatory cytokine milieu in the psoriasis lesion, especially high levels of IL-6 secreted from endothelial cells, DCs and Th17 cells, which inhibit Treg activity and enable infiltrated T effector cells escape from the suppression.^{94,95} Thus, the dysfunctional Treg activity in the blood and psoriatic plaques may eventually result in the reduced restraint and consequent hyperproliferation of psoriatic pathogenic T cells *in vivo*.⁹² It has been noticed that CD4⁺CD25^{high}Foxp3⁺ Tregs can be converted into inflammation-associate Th17 cells under certain condition. Based on these findings, Bovenschen *et al.*⁹⁶ demonstrated that this subset of Tregs from patients with severe psoriasis were more prone to differentiate into IL-17-producing cells compared to healthy controls upon stimulation. Most importantly, they found that there was a specific population of CD4⁺IL-17A⁺Foxp3⁺ cells in the skin lesions, which they assume would probably contribute to the disease development.

T CELL-TARGETED THERAPY IN PSORIASIS

To date, the Food and Drug Administration has approved various biologic agents for psoriasis therapy include an anti-IL-12/IL-23 common chain p40 antibody,^{97,98} TNF- α inhibitors⁹⁹ and T cell-targeted agents. A human antibody against IL-17A or IL-17 receptor is now under phase II clinical trial and has showed a promising therapeutic efficacy.^{100–102} Here, we briefly summarize the recent progress on these biological agents in the treatment of psoriasis.

The pathogenic role of TNF- α in the psoriasis development has made it one of the most important targets for psoriasis therapy. Thus far, there are three Food and Drug Administration-approved anti-TNF- α agents in the market, including etanercept, infliximab and adalimumab and another one, called golimumab, used for the psoriatic arthritis treatment.⁹⁹ Although all these inhibitors showed the significant therapeutic efficacy, the adverse effects cannot be neglected, especially the increased risk for tuberculosis infection during treatment.¹⁰³ Another unexpected side effect of TNF- α antagonist treatment from clinical reports is the induction or exacerbation of psoriatic skin lesions.¹⁰⁴ This could be caused by the dysregulation of cytokine milieu with the increased production of IFN- α and other pro-inflammatory cytokines, such as IL-1 β , IL-6, IL-17, IL-21 and IL-22. Additionally, TNF- α antagonists are also found to enhance Th17 function, but suppress FoxP3⁺ Tregs in the skin in the murine psoriasis-like model.¹⁰⁵ Therefore, the effects of anti-TNF- α agents can be systemic and non-tissue specific, thus caution must be taken when utilizing these agents for therapy.

Recently, the recognition of the importance of IL-23/Th17 axis in psoriasis pathogenesis has prompted the development of new biological agents for psoriasis therapy. Ustekinumab and briakinumab both target IL-12/IL-23 common chain p40 and showed superior efficacy to etanercept in a large clinical study, focusing on the treatment of moderate-to-severe psoriasis.^{97,98,106} However, serious adverse events have been reported during therapy, which might be due to the broad biological effects of IL-23. In this case, targeting the downstream effector cytokine like IL-17 or IL-22 would be a more logical choice.

With great promise, anti-IL-17 antibodies AIN457 (secukinumab) and LY2439821 (ixekizumab) and anti-IL-17 receptor antibody AMG 827 (brodalumab) have shown remarkable therapeutic efficacy in the phase II clinical trials directed towards the treatment of chronic plaque psoriasis.^{100–102} However, their efficacy and safety need to be further assessed in the future.¹⁰⁷ Unfortunately, anti-IL-22 antibody (ILV 095) treatment failed in the phase I clinical trial due to lack of efficacy. Although IL-22 plays a critical role in the murine psoriasis development as well as in psoriasis patients, the significance of targeting IL-22 for the disease treatment remains questionable.

Another important therapeutic approach in the treatment of psoriasis is targeting T cells. In addition to anti-CD4 antibodies and T lymphocyte-associated antigen 4-immunoglobulin, here we focus on Efalizumab and Alefacept, which are two recently developed drugs to inhibit T-cell function.

Efalizumab is a humanized, chimeric monoclonal anti-CD11a antibody that binds to the α subunit of leukocyte function-associated antigen (LFA)-1, thereby blocking the interaction of LFA-1 with intercellular adhesion molecule, leading to a disruption of the interaction between DCs and T cells at tissue sites and in lymph nodes.¹⁰⁸ It also blocks adhesion molecules between T cells and endothelial cells, thus preventing circulating T cells from entering the skin. However, Efalizumab is no longer marketed due to the required boxed warning by the Food and Drug Administration, which highlights the risk of bacterial sepsis, viral meningitis, invasive fungal disease, progressive multifocal leukoencephalopathy¹⁰⁹ and other infection risks after Efalizumab treatment.

Alefacept is a human LFA-3/IgG1 Fc fusion (recombinant) protein that binds to CD2 on memory/effector T cells, selectively blocking the interaction between CD2 on T cells and LFA-3 on antigen-presenting cells, interfering with the function of antigen-presenting cells and T-cell activation.¹⁰⁸ It also induces antibody-dependent cellular cytotoxicity in T cells bound to Alefacept and leads to apoptosis of memory-effector CD45RO-positive T cells in the skin. A recent AWARE (Amevive Wisdom Acquired from Real-World Evidence) study

Table 1 Summary of different subsets of T cells and related cytokines involved in psoriasis pathogenesis

T cell				
Type/subtypes		Cytokine (s) produced	Major role in the pathogenesis of psoriasis	Cytokine-target therapy
CD4	Th1	IFN- γ ^{40,50}	KHEH, SI, DCM	—
		IL-17 ^{50,112}	KHEH, SI, AIRA	Ai ^a , Ly ^a , Am ^a
	Th17	IL-22 ¹¹³	KHEH, SI	IL ^b
		IL-21 ⁵¹	KHEH	—
		IL-6 ⁹⁴	KHEH, Trl	—
		IL-22 ^{114,115}	KHEH, SI	IL ^b
Th22	IL-17 ⁹⁶	KHEH, SI, AIRA, IRD	Ai ^a , Ly ^a , Am ^a	
FoxP3 ⁺ Treg	IL-17 ^{71,116}	KHEH, SI, AIRA	Ai ^a , Ly ^a , Am ^a	
CD8		IL-22 ⁷¹	KHEH, SI	IL ^b
		IFN- γ ¹¹⁶	KHEH, SI, IM, DCM	—
		TNF- α ¹¹⁶	KHEH, DCM	Ad, Et, In, Go ^c
		IL-17 ^{55,112,117}	KHEH, SI, AIRA	Ai ^a , Ly ^a , Am ^a
$\gamma\delta$	Dermal	IL-22 ⁵⁵	KHEH	IL ^b
		TNF- α ⁵⁵	KHEH, DCM	Ad, Et, In, Go ^c
		IL-17 ⁸⁸	KHEH, SI, AIRA	Ai ^a , Ly ^a , Am ^a
NKT		IL-17 ⁸⁸	KHEH, SI, AIRA	Ai ^a , Ly ^a , Am ^a

Abbreviations: Roles in psoriasis pathogenesis: AIRA, acquired immune response amplification; DCM, dendritic cell maturation; IFN, interferon; IRD, immune regulation dysfunction; KHEH, keratinocyte hyperproliferation and epidermal hyperplasia; NKT, natural killer T; SI, skin inflammation; Th, T helper; TNF, tumor-necrosis factor; Trl, Treg inhibition. Therapy: Ad, Adalimumab; Ai, AIN 457; Am, AMG 827—IL-17 receptor targeted; Et, Etanercept; Go, Golimumab; IL, ILV 095; IM, inflammatory migration; In, Infliximab; Ly, LY2439821.

^a In clinical trials.

^b Phase 1 clinical trial discontinued March 2011.

^c Approved for psoriatic arthritis.

supports the safety of alefacept used alone or in combination with other antipsoriatic therapies, in a broad population of chronic plaque psoriasis patients in Canada.¹¹⁰

Another novel T cell-targeted biological drug, called Siplizumab, which is a humanized anti-CD2 monoclonal antibody that interferes with costimulation necessary for T-cell activation and proliferation, has been tested in the clinical trial.¹¹¹ However, two independent randomized, double-blind, placebo-controlled phase II studies showed that Siplizumab only had modest effects and some clinical activity against inflammatory processes in psoriasis patients, suggesting that targeting CD2⁺ cells in psoriasis may not yield a therapeutic benefit.

Table 1 is the summary of different subsets of T cells involved in the pathogenesis of psoriasis, including their released pathogenic cytokines and related biological agents for psoriasis therapy.

FUTURE DIRECTIONS

The new T-cell subsets, like dermal $\gamma\delta$ T cells and Tregs, which are involved in psoriasis pathogenesis, as we mention above, can become the candidates for the future immunotherapy of psoriasis. Current research is focusing on specific subsets of $\gamma\delta$ T cells, such as CCR6-positive V γ 9V δ 2, in hopes of expanding our knowledge of the T cells involved in disease development but also in search for more specific targets for future drug therapies. As therapeutic approaches become more specific towards the major players of psoriasis, keen observations of the unexpected, therapeutic side effects will provide greater knowledge pertaining to these newcomers of psoriasis. As more human genomic data from psoriasis patients become available, investigators can begin looking into the genetic underpinnings to the above T-cell interactions and modulations leading to disease development. Perhaps new areas of study such as immunogenomics will give us

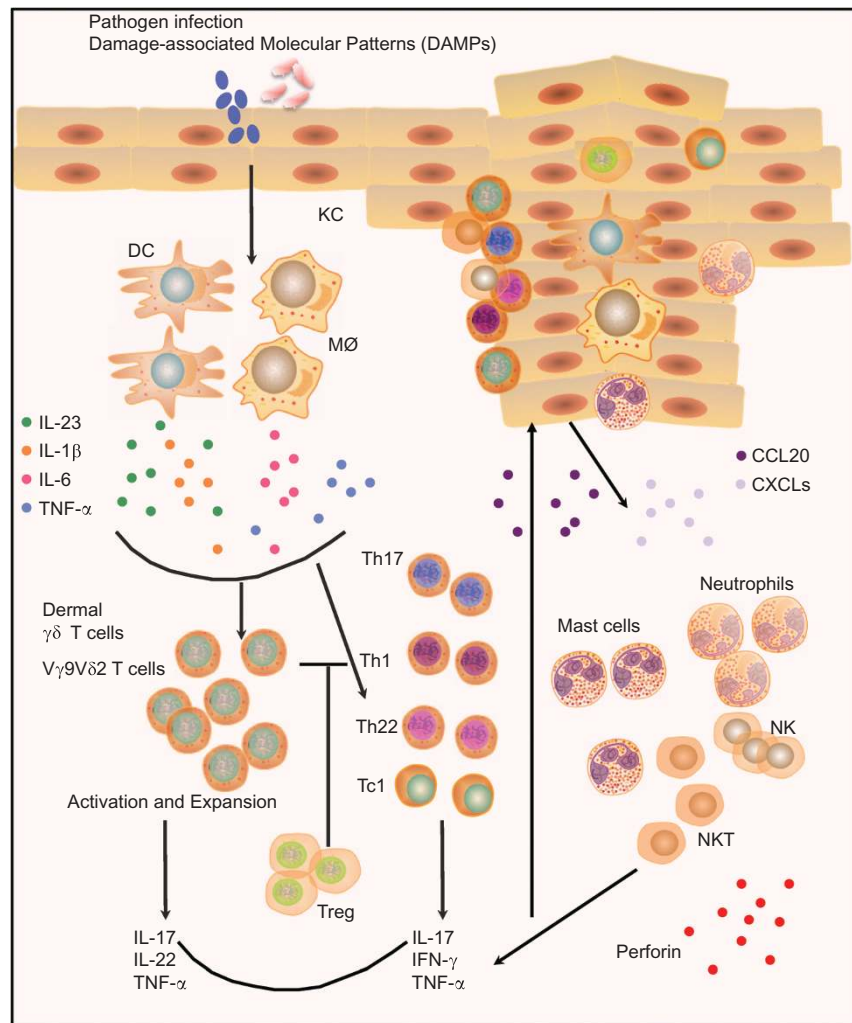


Figure 1 Dysregulated immune responses in psoriasis. Pathogen components or DAMPs activate the DCs and macrophages to produce IL-23, IL-1 β and other pro-inflammatory cytokines including IL-6 and TNF- α . These cytokines induce dermal $\gamma\delta$ T cells activation and expansion to secrete IL-17, IL-22 and TNF- α , which in turn further promote the conventional CD4⁺ T cell-mediated (Th1, Th17 and Th22) and CD8⁺ T cell-mediated (Tc1) acquired immune responses. In addition, skin infiltrating inflammatory cells, such as mast cells, neutrophils, NK cells and NK T cells, also contribute to the disease development *via* producing cytokines (IL-17), antimicrobial peptides and cytotoxic granules. Additionally, the dysfunctional Tregs lose their suppressive activity and some of them are able to convert to Th17 effector cells, further enhancing the inflammatory reaction in the local skin. The pro-inflammatory cytokines and chemokines act on keratinocytes and induce keratinocyte hyperproliferation. The activated keratinocytes also produce some chemokines, such as CCL20 and CXCL1, 3, 8–11, to attract more immune effector cells infiltrating into skin, forming the amplified positive feedback loop, leading to the development of psoriatic lesions. DAMP, damage-associated molecular pattern; DC, dendritic cell; NK, natural killer; Th, T helper; TNF, tumor-necrosis factor; Treg, regulatory T cell.

the tools necessary to clarify elusive problems such as the identity of the autoantigen(s) triggering psoriatic T-cell activation and expansion since these answers could lead to the development of breakthrough immunotherapies.

CONCLUSIONS

Over the past few years, there have been great advances on T cells and their roles in the inflammatory and autoimmune diseases that help us understand more deeply the pathogenesis of psoriasis. Instead of the traditional view regarding psoriasis as a Th1 type disease, it is clearer that Th1, Th17, Treg and Th22 cells interplay with each other and all contribute to the disease development. Additionally, newly identified 'professional' IL-17-producing dermal $\gamma\delta$ T cells also play critical roles in psoriasis pathogenesis. In the schematic model of psoriasis immunopathogenesis depicted in Figure 1, we propose that the pathogens carrying foreign antigens or danger signals first activate the DCs and macrophages to release IL-23, IL-1 β and other pro-inflammatory cytokines. These cytokines can activate dermal $\gamma\delta$ T cells and other IL-17-producing cells to secrete abundant IL-17 further promoting the conventional acquired immune responses. IL-17, IL-22 and TNF- α can act on keratinocytes and induce keratinocyte hyperproliferation. The activated keratinocytes also release chemokines, such as CCL20 and CXCL1, 3, 8–11, to attract more immune effector cells into the skin. These immune effector cells including neutrophils, mast cells, NK and NKT cells further contribute to the pro-inflammatory environment producing cytokines and chemokines. Thus, this amplified positive feedback loop leads to the development of psoriatic lesions.

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- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496–509.
- Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; **370**: 263–271.
- Voorhees JJ. Pathophysiology of psoriasis. *Annu Rev Med* 1977; **28**: 467–473.
- Mueller W, Herrmann B. Cyclosporin A for psoriasis. *N Engl J Med* 1979; **301**: 555.
- Nicolas JF, Chamchick N, Thivolet J, Wijdenes J, Morel P, Revillard JP. CD4 antibody treatment of severe psoriasis. *Lancet* 1991; **338**: 321.
- Prinz J, Braun-Falco O, Meurer M, Daddona P, Reiter C, Rieber P *et al*. Chimaeric CD4 monoclonal antibody in treatment of generalised pustular psoriasis. *Lancet* 1991; **338**: 320–321.
- Abrams JR, Kelley SL, Hayes E, Kikuchi T, Brown MJ, Kang S *et al*. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J Exp Med* 2000; **192**: 681–694.
- Bata-Csorgo Z, Hammerberg C, Voorhees JJ, Cooper KD. Kinetics and regulation of human keratinocyte stem cell growth in short-term primary *ex vivo* culture. Cooperative growth factors from psoriatic lesional T lymphocytes stimulate proliferation among psoriatic uninvolved, but not normal, stem keratinocytes. *J Clin Invest* 1995; **95**: 317–327.
- Wrone-Smith T, Nickoloff BJ. Dermal injection of immunocytes induces psoriasis. *J Clin Invest* 1996; **98**: 1878–1887.
- Nickoloff BJ, Wrone-Smith T. Injection of pre-psoriatic skin with CD4⁺ T cells induces psoriasis. *Am J Pathol* 1999; **155**: 145–158.
- Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. *Arch Dermatol* 1992; **128**: 39–42.
- Gudjonsson JE, Thorarinnsson AM, Sigurgeirsson B, Kristinnsson KG, Valdimarsson H. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. *Br J Dermatol* 2003; **149**: 530–534.
- Lewis HM, Baker BS, Bokth S, Powles AV, Garioch JJ, Valdimarsson H *et al*. Restricted T-cell receptor V beta gene usage in the skin of patients with guttate and chronic plaque psoriasis. *Br J Dermatol* 1993; **129**: 514–520.
- Leung DY, Travers JB, Giorno R, Norris DA, Skinner R, Aelion J *et al*. Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. *J Clin Invest* 1995; **96**: 2106–2112.
- Leung DY, Gately M, Trumble A, Ferguson-Darnell B, Schlievert PM, Picker LJ. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, *via* stimulation of interleukin 12 production. *J Exp Med* 1995; **181**: 747–753.
- Menssen A, Trommler P, Vollmer S, Schendel D, Albert E, Gurtler L *et al*. Evidence for an antigen-specific cellular immune response in skin lesions of patients with psoriasis vulgaris. *J Immunol* 1995; **155**: 4078–4083.
- Chang JC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL *et al*. CD8⁺ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. *Proc Natl Acad Sci USA* 1994; **91**: 9282–9286.
- Prinz JC, Vollmer S, Boehncke WH, Menssen A, Laisney I, Trommler P. Selection of conserved TCR VDJ rearrangements in chronic psoriatic plaques indicates a common antigen in psoriasis vulgaris. *Eur J Immunol* 1999; **29**: 3360–3368.
- Vollmer S, Menssen A, Prinz JC. Dominant lesional T cell receptor rearrangements persist in relapsing psoriasis but are absent from nonlesional skin: evidence for a stable antigen-specific pathogenic T cell response in psoriasis vulgaris. *J Invest Dermatol* 2001; **117**: 1296–1301.
- Prinz JC. Disease mimicry—a pathogenetic concept for T cell-mediated autoimmune disorders triggered by molecular mimicry? *Autoimmun Rev* 2004; **3**: 10–15.
- Prinz JC. Psoriasis vulgaris—a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. *Clin Exp Dermatol* 2001; **26**: 326–332.
- Sigmundsdottir H, Sigurgeirsson B, Troye-Blomberg M, Good MF, Valdimarsson H, Jonsdottir I. Circulating T cells of patients with active psoriasis respond to streptococcal M-peptides sharing sequences with human epidermal keratins. *Scand J Immunol* 1997; **45**: 688–697.
- Gudmundsdottir AS, Sigmundsdottir H, Sigurgeirsson B, Good MF, Valdimarsson H, Jonsdottir I. Is an epitope on keratin 17 a major target for autoreactive T lymphocytes in psoriasis? *Clin Exp Immunol* 1999; **117**: 580–586.
- Johnston A, Gudjonsson JE, Sigmundsdottir H, Love TJ, Valdimarsson H. Peripheral blood T cell responses to keratin peptides that share sequences with streptococcal M proteins are largely restricted to skin-homing CD8⁺ T cells. *Clin Exp Immunol* 2004; **138**: 83–93.
- Besgen P, Trommler P, Vollmer S, Prinz JC. Ezrin, maspin, peroxiredoxin 2, and heat shock protein 27: potential targets of a streptococcal-induced autoimmune response in psoriasis. *J Immunol* 2010; **184**: 5392–5402.
- Brown DW, Baker BS, Ovigne JM, Fischetti VA, Hardman C, Powles AV *et al*. Non-M protein(s) on the cell wall and membrane of group A streptococci induce(s) IFN-gamma production by dermal CD4⁺ T cells in psoriasis. *Arch Dermatol Res* 2001; **293**: 165–170.
- Baker BS, Ovigne JM, Fischetti VA, Powles A, Fry L. Selective response of dermal Th-1 cells to 20–50 kDa streptococcal cell-wall proteins in chronic plaque psoriasis. *Scand J Immunol* 2003; **58**: 335–341.
- Baker BS, Brown DW, Fischetti VA, Porter W, Powles A *et al*. Skin T cell proliferative response to M protein and other cell wall and membrane proteins of group A streptococci in chronic plaque psoriasis. *Clin Exp Immunol* 2001; **124**: 516–521.
- Baker BS, Lamun JD, Powles A, van der Fits L, Voerman JS, Melief MJ *et al*. Peptidoglycan and peptidoglycan-specific Th1 cells in psoriatic skin lesions. *J Pathol* 2006; **209**: 174–181.
- Wang ZM, Liu C, Dziarski R. Chemokines are the main proinflammatory mediators in human monocytes activated by *Staphylococcus aureus*, peptidoglycan, and endotoxin. *J Biol Chem* 2000; **275**: 20260–20267.
- Dziarski R. Peptidoglycan recognition proteins (PGRPs). *Mol Immunol* 2004; **40**: 877–886.
- Valdimarsson H. The genetic basis of psoriasis. *Clin Dermatol* 2007; **25**: 563–567.
- Baker BS, Powles A, Fry L. Peptidoglycan: a major aetiological factor for psoriasis? *Trends Immunol* 2006; **27**: 545–551.
- Conrad C, Boyman O, Tonel G, Tun-Kyi A, Lagner U, de Fougères A *et al*. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nat Med* 2007; **13**: 836–842.
- Valdimarsson H, Thorleifsdottir RH, Sigurdardottir SL, Gudjonsson JE, Johnston A. Psoriasis—as an autoimmune disease caused by molecular mimicry. *Trends Immunol* 2009; **30**: 494–501.
- Cai YH, Lu ZY, Shi RF, Xue F, Chen XY, Pan M *et al*. Enhanced proliferation and activation of peripheral blood mononuclear cells in patients with psoriasis vulgaris mediated by streptococcal antigen with bacterial DNA. *J Invest Dermatol* 2009; **129**: 2653–2660.
- Schlaak JF, Buslau M, Jochum W, Hermann E, Girndt M, Gallati H *et al*. T cells involved in psoriasis vulgaris belong to the Th1 subset. *J Invest Dermatol* 1994; **102**: 145–149.
- Austin LM, Ozawa M, Kikuchi T, Walters IB, Krueger JG. The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: a type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients. *J Invest Dermatol* 1999; **113**: 752–759.
- Friedrich M, Krammig S, Henze M, Docke WD, Sterry W, Asadullah K. Flow cytometric characterization of lesional T cells in psoriasis: intracellular cytokine and surface antigen expression indicates an activated, memory/effector type 1 immunophenotype. *Arch Dermatol Res* 2000; **292**: 519–521.
- Lew W, Bowcock AM, Krueger JG. Psoriasis vulgaris: cutaneous lymphoid tissue supports T-cell activation and "Type 1" inflammatory gene expression. *Trends Immunol* 2004; **25**: 295–305.

- 41 Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007; **25**: 821–852.
- 42 Steinman L. A brief history of T_H17 , the first major revision in the T_H1/T_H2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**: 139–145.
- 43 Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol* 2009; **27**: 485–517.
- 44 Kastelein RA, Hunter CA, Cua DJ. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 2007; **25**: 221–242.
- 45 Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupe P, Barillot E *et al*. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T_H17 responses. *Nat Immunol* 2008; **9**: 650–657.
- 46 Boniface K, Blom B, Liu YJ, de Waal Malefyt R. From interleukin-23 to T-helper 17 cells: human T-helper cell differentiation revisited. *Immunol Rev* 2008; **226**: 132–146.
- 47 McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM *et al*. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells *in vivo*. *Nat Immunol* 2009; **10**: 314–324.
- 48 Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B *et al*. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 2000; **13**: 715–725.
- 49 Boniface K, Guignouard E, Pedretti N, Garcia M, Delwail A, Bernard FX *et al*. A role for T cell-derived interleukin 22 in psoriatic skin inflammation. *Clin Exp Immunol* 2007; **150**: 407–415.
- 50 Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS *et al*. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 2008; **128**: 1207–1211.
- 51 Caruso R, Botti E, Sarra M, Esposito M, Stolfi C, Diluvio L *et al*. Involvement of interleukin-21 in the epidermal hyperplasia of psoriasis. *Nat Med* 2009; **15**: 1013–1015.
- 52 Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *J Invest Dermatol* 2010; **130**: 1373–1383.
- 53 Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F *et al*. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; **199**: 125–130.
- 54 Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. *In vitro* and *in situ* expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol* 2006; **176**: 1908–1915.
- 55 Cai Y, Shen X, Ding C, Qi C, Li K, Li X *et al*. Pivotal role of dermal IL-17-producing gammadelta T cells in skin inflammation. *Immunity* 2011; **35**: 596–610.
- 56 Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S *et al*. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med* 2006; **203**: 2577–2587.
- 57 Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J *et al*. Interleukin-22, a T_H17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; **445**: 648–651.
- 58 Hedrick MN, Lonsdorf AS, Shirakawa AK, Richard Lee CC, Liao F, Singh SP *et al*. CCR6 is required for IL-23-induced psoriasis-like inflammation in mice. *J Clin Invest* 2009; **119**: 2317–2329.
- 59 Rizzo HL, Kagami S, Phillips KG, Kurtz SE, Jacques SL, Blauvelt A. IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A. *J Immunol* 2011; **186**: 1495–1502.
- 60 van Belle AB, de Heusch M, Lemaire MM, Hendrickx E, Warnier G, Renauld JC *et al*. IL-22 is required for imiquimod-induced psoriasisform skin inflammation in mice. *J Immunol* 2012; **188**: 462–469.
- 61 Shi X, Jin L, Dang E, Chang T, Feng Z, Liu Y *et al*. IL-17A upregulates keratin 17 expression in keratinocytes through STAT1- and STAT3-dependent mechanisms. *J Invest Dermatol* 2011; **131**: 2401–2408.
- 62 Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M *et al*. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006; **203**: 2271–2279.
- 63 Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD *et al*. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007; **8**: 950–957.
- 64 Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I *et al*. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008; **159**: 1092–1102.
- 65 Kryczek I, Bruce AT, Gudjonsson JE, Johnston A, Aphale A, Vatan L *et al*. Induction of IL-17⁺ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. *J Immunol* 2008; **181**: 4733–4741.
- 66 Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC *et al*. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol* 2009; **129**: 79–88.
- 67 Johnson-Huang LM, Suarez-Farinas M, Pierson KC, Fuentes-Duculan J, Cueto I, Lentini T *et al*. A single intradermal injection of IFN-gamma induces an inflammatory state in both non-lesional psoriatic and healthy skin. *J Invest Dermatol* 2012; **132**: 1177–1187.
- 68 Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T_H17 , T_H1 and T_H2 cells. *Nat Immunol* 2009; **10**: 864–871.
- 69 Duhon T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. *Nat Immunol* 2009; **10**: 857–863.
- 70 Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S *et al*. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest* 2009; **119**: 3573–3585.
- 71 Res PC, Piskin G, de Boer OJ, van der Loos CM, Teeling P, Bos JD *et al*. Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. *PLoS ONE* 2010; **5**: e14108.
- 72 Bergstresser PR, Tigelaar RE, Dees JH, Streilein JW. Thy-1 antigen-bearing dendritic cells populate murine epidermis. *J Invest Dermatol* 1983; **81**: 286–288.
- 73 Hayday AC. $\gamma\delta$ cells: a right time and a right place for a conserved third way of protection. *Annu Rev Immunol* 2000; **18**: 975–1026.
- 74 Asarnow DM, Kuziel WA, Bonyhadi M, Tigelaar RE, Tucker PW, Allison JP. Limited diversity of gamma delta antigen receptor genes of Thy-1⁺ dendritic epidermal cells. *Cell* 1988; **55**: 837–847.
- 75 Jameson J, Havran WL. Skin gammadelta T-cell functions in homeostasis and wound healing. *Immunol Rev* 2007; **215**: 114–122.
- 76 Havran WL, Jameson JM. Epidermal T cells and wound healing. *J Immunol* 2010; **184**: 5423–5428.
- 77 Gray EE, Suzuki K, Cyster JG. Cutting edge: identification of a motile IL-17-producing gammadelta T cell population in the dermis. *J Immunol* 2011; **186**: 6091–6095.
- 78 Sumaria N, Roediger B, Ng LG, Qin J, Pinto R, Cavanagh LL *et al*. Cutaneous immunosurveillance by self-renewing dermal gammadelta T cells. *J Exp Med* 2011; **208**: 505–518.
- 79 O'Brien RL, Roark CL, Born WK. IL-17-producing gammadelta T cells. *Eur J Immunol* 2009; **39**: 662–666.
- 80 Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. *Immunity* 2009; **31**: 321–330.
- 81 Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. *Immunity* 2009; **31**: 331–341.
- 82 Mabuchi T, Takekoshi T, Hwang ST. Epidermal CCR6⁺ $\gamma\delta$ T cells are major producers of IL-22 and IL-17 in a murine model of psoriasisform dermatitis. *J Immunol* 2011; **187**: 5026–5031.
- 83 Laggner U, Di Meglio P, Perera GK, Hundhausen C, Lacy KE, Ali N *et al*. Identification of a novel proinflammatory human skin-homing V γ 9V δ 2 T cell subset with a potential role in psoriasis. *J Immunol* 2011; **187**: 2783–2793.
- 84 Nicklolf BJ, Wrono-Smith T, Bonish B, Porcelli SA. Response of murine and normal human skin to injection of allogeneic blood-derived psoriatic immunocytes: detection of T cells expressing receptors typically present on natural killer cells, including CD94, CD158, and CD161. *Arch Dermatol* 1999; **135**: 546–552.
- 85 Nicklolf BJ, Bonish B, Huang BB, Porcelli SA. Characterization of a T cell line bearing natural killer receptors and capable of creating psoriasis in a SCID mouse model system. *J Dermatol Sci* 2000; **24**: 212–225.
- 86 Ottaviani C, Nasorri F, Bedini C, de Pita O, Girolomoni G, Cavani A. CD56^{bright}CD16⁻ NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation. *Eur J Immunol* 2006; **36**: 118–128.
- 87 Kastelan M, Prpic Massari L, Gruber F, Zamolo G, Zauhar G, Coklo M *et al*. Perforin expression is upregulated in the epidermis of psoriatic lesions. *Br J Dermatol* 2004; **151**: 831–836.
- 88 Cosmi L, de Palma R, Santarlasci V, Maggi L, Capone M, Frosali F *et al*. Human interleukin 17-producing cells originate from a CD161⁺CD4⁺ T cell precursor. *J Exp Med* 2008; **205**: 1903–1916.
- 89 Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S *et al*. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol* 2011; **187**: 490–500.
- 90 Buonocore S, Ahern PP, Uhlig HH, Ivanov II, Littman DR, Maloy KJ *et al*. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* 2010; **464**: 1371–1375.
- 91 Wing K, Sakaguchi S. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat Immunol* 2010; **11**: 7–13.
- 92 Sugiyama H, Gyulai R, Toichi E, Garaczi E, Shimada S, Stevens SR *et al*. Dysfunctional blood and target tissue CD4⁺CD25^{high} regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. *J Immunol* 2005; **174**: 164–173.
- 93 Wang H, Peters T, Sindrilaru A, Kess D, Oreshkova T, Yu XZ *et al*. TGF-beta-dependent suppressive function of Tregs requires wild-type levels of CD18 in a mouse model of psoriasis. *J Clin Invest* 2008; **118**: 2629–2639.
- 94 Goodman WA, Levine AD, Massari JV, Sugiyama H, McCormick TS, Cooper KD. IL-6 signaling in psoriasis prevents immune suppression by regulatory T cells. *J Immunol* 2009; **183**: 3170–3176.
- 95 Clark RA. Skin-resident T cells: the ups and downs of on site immunity. *J Invest Dermatol* 2010; **130**: 362–370.
- 96 Bovenschen HJ, van de Kerkhof PC, van Erp PE, Woestenenk R, Joosten I, Koenen HJ. Foxp3⁺ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. *J Invest Dermatol* 2011; **131**: 1853–1860.
- 97 Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N *et al*. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; **362**: 118–128.

- 98 Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br J Dermatol* 2011; **165**: 661–668.
- 99 Kircik LH, del Rosso JQ. Anti-TNF agents for the treatment of psoriasis. *J Drugs Dermatol* 2009; **8**: 546–559.
- 100 Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G *et al*. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010; **2**: 52ra72.
- 101 Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E *et al*. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 2012; **366**: 1190–1199.
- 102 Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G *et al*. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; **366**: 1181–1189.
- 103 Bachmann F, Nast A, Sterry W, Philipp S. Safety and efficacy of the tumor necrosis factor antagonists. *Semin Cutan Med Surg* 2010; **29**: 35–47.
- 104 Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum* 2010; **40**: 233–240.
- 105 Ma HL, Napierata L, Stedman N, Benoit S, Collins M, Nickerson-Nutter C *et al*. Tumor necrosis factor alpha blockade exacerbates murine psoriasis-like disease by enhancing Th17 function and decreasing expansion of Treg cells. *Arthritis Rheum* 2010; **62**: 430–440.
- 106 Gordon KB, Langley RG, Gottlieb AB, Papp KA, Krueger GG, Strober BE *et al*. A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. *J Invest Dermatol* 2012; **132**: 304–314.
- 107 Waisman A. To be 17 again—anti-interleukin-17 treatment for psoriasis. *N Engl J Med* 2012; **366**: 1251–1252.
- 108 Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet* 2007; **370**: 272–284.
- 109 Korman BD, Tyler KL, Korman NJ. Progressive multifocal leukoencephalopathy, efalizumab, and immunosuppression: a cautionary tale for dermatologists. *Arch Dermatol* 2009; **145**: 937–942.
- 110 Bissonnette R, Searles G, Landells I, Shear NH, Papp K, Lui H *et al*. The AWARE study: methodology and baseline characteristics. *J Cutan Med Surg* 2009; Suppl 3, S113–S121.
- 111 Bissonnette R, Langley RG, Papp K, Matheson R, Toth D, Hultquist M *et al*. Humanized anti-CD2 monoclonal antibody treatment of plaque psoriasis: efficacy and pharmacodynamic results of two randomized, double-blind, placebo-controlled studies of intravenous and subcutaneous siplizumab. *Arch Dermatol Res* 2009; **301**: 429–442.
- 112 Raychaudhuri SP. Role of IL-17 in psoriasis and psoriatic arthritis. *Clin Rev Allergy Immunol* 2012.
- 113 Nograles KE, Davidovici B, Krueger JG. New insights in the immunologic basis of psoriasis. *Semin Cutan Med Surg* 2010; **29**: 3–9.
- 114 Sa SM, Valdez PA, Wu J, Jung K, Zhong F, Hall L *et al*. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. *J Immunol* 2007; **178**: 2229–2240.
- 115 Wolk K, Witte E, Wallace E, Docke WD, Kunz S, Asadullah K *et al*. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Eur J Immunol* 2006; **36**: 1309–1323.
- 116 Ortega C, Fernandez AS, Carrillo JM, Romero P, Molina IJ, Moreno JC *et al*. IL-17-producing CD8⁺ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. *J Leukoc Biol* 2009; **86**: 435–443.
- 117 Raychaudhuri SP, Raychaudhuri SK, Genovese MC. IL-17 receptor and its functional significance in psoriatic arthritis. *Mol Cell Biochem* 2012; **359**: 419–429.