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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 γδ 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) Vβ 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 psoriasiform 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 $IL\text{-}17^+$ 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 (γδ) T cells, natural killer (NK) cells and natural killer T (NKT) cells and their potential roles in psoriasis.

Murine skin contains abundant γδ T cells in the epidermis, called dendritic epidermal γδ T cells.[72,73] The development and function of dendritic epidermal γδ T cells have been well defined for decades.[74–76] Recently, three laboratories including ours have identified a novel γδ T-cell subset in the dermis.[55,77,78] Unlike dendritic epidermal γδ T cells and conventional αβ T cells, dermal γδ T cells constitutively express IL-23 receptor, CCR6 and transcriptional factor RORγt. 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 γδ 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-1β or danger signal stimulation even in the absence of TCR ligation.[79–81] Thus, γδ 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 γδ T cells are also found very critical in the psoriasis pathogenesis.[55] In TCR δ-deficient ($TCRd^{-/-}$) 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 $TCRd^{-/-}$ mice, but they claimed there were specific epidermal CCR6 positive γδ 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 γδ T cells might migrate into the epidermis during the inflammation. This notion is supported by the finding that this subset of γδ T cells is scarce in epidermis under a steady condition.[55] We also found that dermal γδ T cells expanded upon IL-23 stimulation. Importantly, high frequency of γδ T cells was found in the lesions of psoriatic patients, which closely link the murine model system to the clinics. These γδ 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 Vγ9Vδ2 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 γδ 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 γδ 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 γδ 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 γδ 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 autoimmune 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 $CD4^+IL\text{-}17A^+Foxp3^+$ 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 inhibitors[99] 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-1β, 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 leukoencephalopathy[109] and other infection risks after Efalizumab treatment.

Alefacept is a human LFA-3/IgG1 F*c* 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	—
	Th17	IL-17[50,112]	KHEH, SI, AIRA	Ai[a], Ly[a], Am[a]
		IL-22[113]	KHEH, SI	IL[b]
		IL-21[51]	KHEH	—
		IL-6[94]	KHEH, TrI	—
	Th22	IL-22[114,115]	KHEH, SI	IL[b]
	FoxP3$^+$ Treg	IL-17[96]	KHEH, SI, AIRA, IRD	Ai[a], Ly[a], Am[a]
CD8		IL-17[71,116]	KHEH, SI, AIRA	Ai[a], Ly[a], Am[a]
		IL-22[71]	KHEH, SI	IL[b]
		IFN-γ[116]	KHEH, SI, IM, DCM	—
		TNF-α[116]	KHEM, DCM	Ad, Et, In, Go[c]
γδ	Dermal	IL-17[55,112,117]	KHEH, SI, AIRA	Ai[a], Ly[a], Am[a]
		IL-22[55]	KHEH	IL[b]
		TNF-α[55]	KHEM, DCM	Ad, Et, In, Go[c]
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; TrI, 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 γδ 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 γδ T cells, such as CCR6-positive Vγ9Vδ2, 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

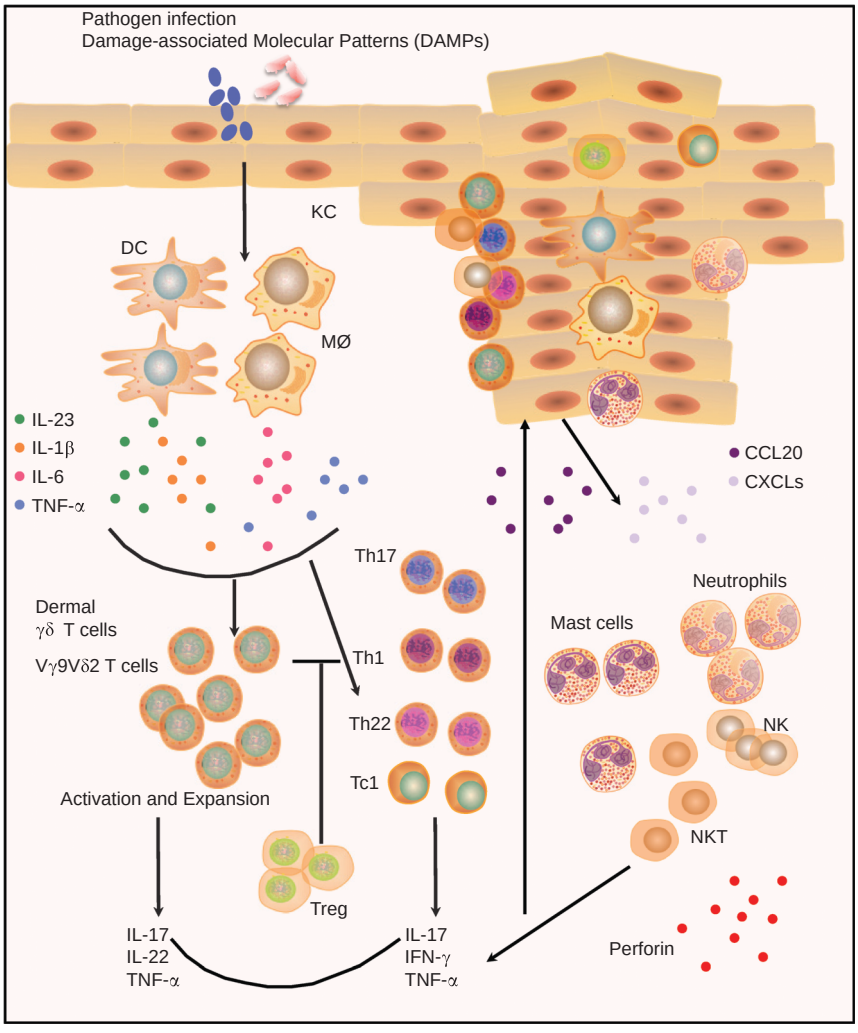

Figure 1 Dysregulated immune responses in psoriasis. Pathogen components or DAMPs activate the DCs and macrophages to produce IL-23, IL-1β and other pro-inflammatory cytokines including IL-6 and TNF-α. These cytokines induce dermal γδ T cells activation and expansion to secrete IL-17, IL-22 and TNF-α, 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-inflamamtory 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 γδ 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-1β and other pro-inflammatory cytokines. These cytokines can activate dermal γδ 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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