DERMATOLOGICA SINICA 30 (2012) 136–141

Contents lists available at SciVerse ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

REVIEW ARTICLE

T helper type 17 in psoriasis: From basic immunology to clinical practice

Hsien-Yi Chiu [1,2], Yu-Pin Cheng [1,2], Tsen-Fang Tsai [1,*]

[1] Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[2] Department of Dermatology, National Taiwan University Hospital, Hsin-Chu Branch, Hsin-Chu, Taiwan

ARTICLE INFO

Article history:
Received: Jun 28, 2012
Revised: Aug 13, 2012
Accepted: Aug 16, 2012

Keywords:
biologics
interleukin-17
interleukin-23
psoriasis
T helper type 17

ABSTRACT

Psoriasis is a chronic inflammatory disease mediated by a complex interplay between immune system and keratinocytes. Initially considered as a keratinocyte proliferation/differentiation disorder, an immune dysregulation was confirmed after the successful treatment of psoriasis with cyclosporine. The ying–yang theory, or T helper type 1 (Th1)/Th2 concept, was then introduced to explain the rarity of atopic dermatitis in patients with psoriasis and the aggravation of psoriasis after interferon-γ treatment. However, recent advances have revised the Th1/Th2 paradigm after the discovery of a novel subset of T cells, called Th17 cells. Th17 cells produce interleukin (IL)-17 and IL-22, and have other important downstream proinflammatory effects on skin, leading to clinical and pathological features typical of psoriasis. Nowadays, emerging evidence suggests integrative and complicated inflammatory circuits among Th1 and Th17 cells and keratinocytes in the pathogenesis of psoriasis, with Th17 cells playing a central role. Herein, we review the biology of Th17 cells as well as the reciprocal interplay between Th17 and regulatory T cells in psoriasis. Integration of the IL-23/Th17 axis into a revised concept of psoriasis has already been translated into novel therapeutic strategies. Studies investigating the effect and molecular mechanism of conventional and biological therapy for psoriasis on the IL-23/Th17 pathway were also discussed.

Introduction: from Th1/Th2 to Th17

Traditionally, $CD4^+$ T cells have classically been separated into two dominant effector cell populations: T helper type 1 (Th1) and type 2 (Th2).[1] However, during recent years, emerging studies, both in mice and in human, have shown that interleukin (IL)-17-producing T cells represents a new lineage of effector CD4 T cells, Th17 cells.[2] IL-17 was first identified in rodent T-cell hybridoma.[3] Later, IL-23 was shown to mediate the expansion of IL-17-producing cells, and the finding led to the discovery of Th17 cells.[4–6] The concept of Th17 cells as a distinct subset of T cells was further strengthened by the delineation of its unique differentiation pathway. Differentiation of naïve T cells into Th17 cells depends on a mechanism that is different from the signals driving the development of Th1 [T-bet, signal transducer and activator of transcription (STAT) 4, and STAT1] and Th2 cells [GATA-binding protein 3 (GATA3), c-MAF, and STAT6]. Interferon-γ (IFN-γ), as well as IL-12 and IL-4, drives naïve T cells into Th1 and Th2 responses separately, whereas IFN-γ and IL-4 potently inhibit the development of murine Th17 cells.[2,7] Langrish et al[5] showed that proliferation of Th17 cells highly depends on IL-23. Data presented by Dong[8] and Murphy et al[9] indicated that inducible T-cell costimulator and IL-23 were required for IL-17 expression, but not for IFN-γ expression, in the mice models of experimental autoimmune encephalomyelitis and collagen-induced arthritis. Like Th1 and Th2 cells, Th17 cells produce a group of distinctive cytokines. Th17 cells do not produce IFN-γ or IL-4; instead, they produce IL-17 and express the IL-23 receptor (IL-23R).[5,7] Additionally, chemokine (C-C motif) receptor (CCR)4 and CCR6 are major chemokine receptors involved in Th17 response, which are different from predominant expression of CXCR6, CCR5, and CXCR3 in Th1 cells as well as CCR3, CCR4, and CCR8 in Th2 cells, respectively.[10] Based on the unique priming cytokines, lineage-specific transcriptional regulators, cytokine products, and cytokine receptors, Th17 cells are widely accepted as a separate and early lineage of effector T cells, rather than cells differentiating directly from Th1 or Th2 cells.

Basics of Th17

A significant amount of both clinical and experimental data has established Th17 cells as a new lineage of Th cells. Differentiation of

* Corresponding author. Department of Dermatology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan. Tel.: +886 2 23562141; fax: +886 2 23934177.
E-mail address: tftsai@yahoo.com (T.-F. Tsai).

1027-8117/$ – see front matter
http://dx.doi.org/10.1016/j.dsi.2012.08.002

Th cells is instructed by the innate immune system, which provides costimulatory molecules and cytokines that mediate the development of a specific Th-cell lineage in response to antigens. Although IL-23 was originally shown to be important for the proliferation of Th17 cells, compelling scientific evidence suggested that IL-23 alone was not sufficient for the initiation of Th17 differentiation from naïve T cells as they did not express IL-23R.[5,11,12] A concomitant presence of transforming growth factor-β (TGF-β) and at least one proinflammatory cytokine, such as IL-6, IL-1β, IL-23, or IL-21, was necessary for the differentiation of naïve T cells to Th17 cells.[13–15] After induction by TGF-β and proinflammatory cytokines, differentiating and differentiated Th17 cells upregulate the expressions of IL-23R and IL-1R1, which may mediate or maintain the final lineage specification or induce the proliferation of pre-committed Th17 cells. Additionally, Langrish et al[5] and Park et al[7] showed that IL-23 had little effect on fully differentiated Th1 or Th2 cells, and Th1 or Th2 development apparatus (IFN-γ, STAT1, and IL-4) inhibited the development of Th17 cells. Mature Th17 cells were resistant to suppression by Th1 or Th2 cytokines.[5,7] These studies suggest that the differentiation of $CD4^+$ T cells to Th17 cells starts at a point preceding commitment to the Th1 or Th2 lineages.

Integrated signals from cytokine receptors, T-cell receptors, and costimulatory molecules lead to the expression lineage-specific transcription factors that contribute significantly to the differentiation of different Th cells. Transcription factors and their regulators T-bet, H2.0-like homeobox, STAT1, and STAT4 specify Th1 cell fate, whereas GATA3, c-MAF, STAT6 govern Th2 cell differentiation.[8] Neither the transcriptional factors implicated in Th1 differentiationnor those in Th2 differentiation were involved in Th17 cell development. Recently, two transcriptional factors, retinoid-related orphan receptor (ROR) γt and RORα, were shown to play key roles in the differentiation program of Th17 cells.[16,17] TGF-β and IL-6 induce the expression of RORγt and RORα in a STAT3-dependent manner. STAT3 protein regulates Th17 differentiation, at least in part, through the induction of lineage-specific transcription factors and IL-23 also signals through STAT3 in Th17 cells.[18,19] On the contrary, RORγt-deficient T cells were defective in Th17 cell differentiation.[16,18,20] Mice with RORγt-deficient T cells lack tissue-infiltrating Th17 cells and have attenuated autoimmune diseases.[16] In addition to ROR, IFN regulatory factor 4,[21] runt-related transcription factor 1,[22] and ATF-like basic leucine zipper transcription factor[23] were also shown to be essential for Th17 cell differentiation.

Cytokines produced and secreted by Th17 cells include IL-6, IL-17A, IL-17F, IL-21, IL-22, and tumor necrosis factor (TNF)-α.[8] IL-17 family, for which the Th17 cells lineage is named, consists of six cytokines (IL-17A–F).IL-17A, IL-17B, IL-17C, and IL17F, but not IL-17E, have proinflammatory properties, can induce cytokines such as TNF and IL-1β, and promote neutrophil migration.[24] Although Th17 cells are the major source of IL-17A, it can be produced by a wide range of cell types, including $CD8^+$ cells, γδ-TCR^+ cells, neutrophils, B cells, and natural killer T cells.[25–29] Functional analysis of IL-17A has suggested that it plays an important and unique role in the development of autoimmunity, inflammation, tumors, and host protection against specific pathogens, such as *Candida*,[30] Mycobacterium,[6] and *Klebsiella*.[31] IL-17F shares 50% sequence homology with IL-17A and is mainly involved in mucosal host defense mechanism.[24] Although the ability of IL-17B, IL-17C, and IL-17D to express proinflammatory cytokines is similar to that of IL-17A and IL-17F, the role of the former in the immune system has not yet been fully elucidated.[24] IL-17E is not produced by Th17 cells but produced by Th2 cells, cecal patch $CD4^+$ and $CD8^+$ T cells, mast cells, and eosinophils.[24] It enhances Th2 cell immune response by inducing IL-4, IL-5, IL-13, IgE production, and eosinophilia, contributing to the host defense against nematodes and allergic disorders.[24]

Circumstantial evidence also suggests that Th17 cells regulate the development of autoimmune diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma.[5,8,32] Emerging data also investigate the role of Th17 cells in the etiopathogenesis of periodontal disease.[33] In 1998, Teunissen et al[34] showed detectable levels of IL-17 mRNA in lesional psoriatic skin, but not in nonlesional skin. Subsequent studies also demonstrated increased expression of IL-17A, IL-17C, IL-17F, and IL-23 subunits in lesional psoriatic skin compared with nonlesional and normal skin.[35] Kagami et al[36] demonstrated that circulating Th17, Th22, and Th1 cells were increased in psoriasis patients, and blood levels of Th17 and Th1 cells also decreased after therapy with TNF-α antagonist (infliximab). Intradermal injection of IL-23 in mice led to lesions with histopathological features resembling psoriasis.[37] $CD4^+$ Th17 cells were present in higher numbers in psoriatic lesions than in healthy skin and decreased after treatment.[38] Zaba et al[39] showed that psoriatic dermal dendritic cells could induce T-cell proliferation, and polarize T cells to become Th17 and Th1 cells. Both IL-17A and IL-22 induce keratinocyte expressing chemokine (C-C motif) ligand 20 (CCL20), which attracts Th17 cells to sites of inflammation via CCL20–CCR6 signaling and drives epidermal acanthosis, linking the IL23/Th17 axis with pathology of psoriasis.[40] Furthermore, human genetic studies have shown multiple IL-17-related genes, including IL-23A, IL-23R, IL-12B, TNFAIP3, and tyrosine kinase 2 (TYK2), as risk alleles for psoriasis.[41,42] IL-23A and IL-23R are specific to IL-23 signaling, and TYK2 is a signal kinase downstream of IL-12 and IL-23. TNFAIP3 functions as a key regulator of NF-κB pathway, which is also the downstream target of IL-17 receptor signaling. IL-12B gene expresses the shared IL-12/23p40 subunit with IL-23.[42] Collectively, these data have confirmed the central role of IL23/Th17 in the pathogenesis of psoriasis.

IL-21 is not only a Th17 cytokine but also a differentiation factor for Th17 cells when present alone or with IL-6 or TGF-β.[18] Loss of IL-21 or its receptor had decreased Th17 cells in mice, which resulted in a large increase in T-regulatory cells (T-reg) *in vitro*.[18,20,43] Additionally, IL-21 as well as TGF-β also acts in an autocrine manner to promote Th17 differentiation.[43–45]

IL-23, a member of IL-12 family, is a heterodimeric cytokine formed by a p40 chain, which is shared with IL-12, and a unique p19 chain. IL-23 is secreted by dendritic cells, macrophages, other antigen-presenting cells as well as keratinocytes,[46] and plays a pivotal role in the survival and proliferation of Th17 cells after priming with TGF-β and IL-6.[5,9] In IL-23-deficient mice, experimental autoimmune encephalomyelitis resistance correlates with the absence of IL-17-producing T cells.[5]

In addition to $CD4^+$ Th cells, IL-17 can also be produced by $CD8^+$ T cells, called type 17 cytotoxic T cells (Tc17). Tc17 cells are characterized by sharing some, but not all, phenotypical and molecular features with both Th17 and Th1 cells. They express Th17 population-selective features, such as CCR6, IL-23R, and RORγt transcription factor.[47] Ortega et al[47] showed that Tc17 cells from psoriasis-inflamed skin tissue produced IL-17, IL-21, and IL-22 (Th17-related cytokines) as well as TNF-α and IFN-γ (Th1-related cytokines). Tc17 cells also displayed T-cell receptor/CD3-mediated cytotoxic abilities to kill target cells.[47] Notably, when IL-12 was added to the Tc17 cell culture, the T-bet (Th1-associated transcription factor) was clearly upregulated.[48] Recent studies have suggested that Tc17 cells also play a role in the pathogenesis of psoriasis. Res et al[49] reported that psoriatic skin contained a T-cell infiltrate with a significant increased percentage of Tc17 cells compared to normal skin. The increase of Tc17 cells was most pronounced in the psoriatic epidermis, which reinforced the distinct functional role of Tc17 cells in psoriasis.[49]