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Chapter

Effects of IL-17 on Epidermal Development

Emi Sato and Shinichi Imafuku

Abstract

Immunotherapies targeting interleukin 17 (IL-17) have a strong effect on plaque psoriasis. However, many previous studies on IL-17 focused only on the T-helper 17 (Th17) immune response, and a few studies have reported that IL-17A may affect psoriatic epidermal structure. IL-17 includes six family members, namely IL-17A–F, which are involved in a wide variety of biological responses. IL-17A is produced mainly by Th17 cells or group 3 innate lymphoid cells (ILC3), while IL-17C is locally produced by epithelial cells, such as keratinocytes. In contrast to IL-17C, which is locally produced in various cells such as keratinocytes, it is predicted that IL-17A, which is produced by limited cells and has systemic effects, has different roles in epidermal development. For example, several research studies have shown that IL-17A affects terminal differentiation of epidermis by suppressing the expression of filaggrin or loricrin in keratinocytes. On the other hand, IL-17C, which is produced by keratinocytes themselves, does not have as strong as an effect on epidermal development as IL-17A. In this chapter, we summarized the effects of IL-17A and other IL-17 members on epidermal development and their comprehensive roles based on previously reported papers.

Keywords: psoriasis, IL-17, epidermal structure, terminal differentiation genes

1. Introduction

Since 2003, biologics targeting inflammatory cytokines have been used to treat a wide range of diseases, especially those in which excessive autoimmunity is involved in the pathogenesis, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and atopic dermatitis [1–6]. Before biologics targeting specific pro-inflammatory cytokines were introduced, the mechanisms involved in the pathogenesis of diseases were understood to a certain extent. However, once the therapy was actually started, various contradictions were seen. For example, psoriasis is thought to be mainly caused by T-helper 1 (Th1) and T-helper 17 (Th17) cells [7–9]; therefore, treatments that inhibit the differentiation of undifferentiated T-cells into Th1 and Th17 (e.g., CD80/86, CD2, CD11a, and RORγT inhibitors) were expected to be the most effective in correcting the root of the disease. However, contrary to expectations, biologics targeting interleukin 17 (IL-17) are actually considered to be the most effective treatment for psoriasis [1]. In other words, direct inhibition of terminal IL-17 is more effective than inhibition of Th17 differentiation in psoriasis, as suggested by actual patient data. This suggested that IL-17, especially IL-17A, might be produced by cells other than Th17 cells. Subsequent studies also revealed that group 3 innate lymphoid cells (ILC3) and γδ T-cells in the

skin produce IL-17A [10–12]. Although new facts may be revealed in the future, this chapter summarizes our current knowledge of the role of IL-17 and its sources of production, with a focus on epidermal development.

2. Which cells produce IL-17 in the skin?

IL-17 is a homodimeric glycoprotein consisting of 20–30 kDa peptides. The IL-17 family can be divided into six family members, IL-17A-IL-17F (**Table 1**). This section summarizes the roles of each IL-17 member and the cells that produce them (**Figure 1**).

2.1 IL-17A

Th17 cells are thought to be the major producers of IL-17A. However, the biologics that target IL-17A have a greater effect on psoriasis compared with subunits, such as p40, that are required for differentiation into Th17 [13]. This suggests that cells other than Th17 cells are also responsible for IL-17A production. Non-Th17 cells that have been reported in the past include: neutrophils [14], mast cells [15, 16], CD8+ T-cells [17], αβ T-cells [18], γδ T-cells [12], and innate lymphoid cells (ILC) [10, 11]. IL-17A has effects on various cells, such as fibroblasts, keratinocytes, endothelial cells, and macrophages, to induce release of inflammatory cytokines/chemokines such as IL-6, TNF-α, and IL-8, as well as promoting neutrophil migration to induce inflammation [19]. In particular, IL-17A induces granulocyte-colony stimulating factor (G-CSF) and IL-8, cytokines that are strongly involved in the activation of neutrophils [19–21]. The inflammation that is induced by IL-17A contributes greatly to the defense against bacterial, fungal, and viral infections, but excessive inflammation can lead to autoimmune diseases and the creation of unfortunate conditions in the skin, such as psoriasis and hidradenitis suppurativa (HS), as described below. Additionally, IL-17A is directly involved in epidermal differentiation, as described below, and this may also be related to the formation of a pathological epidermis, such as psoriasis [22–24].

Ligand	Receptor	Producer cells	Effects
IL-17A	IL-17RA/RC	T cells (RORγt+ (**Th17,Tc17**), γδ+, αβ+), innate lymphoid cells (**ILC3**), neutrophils, and mast cells	protection against pathogens and inflammation, epidermal proliferation, and differentiation
IL-17B	IL-17RB	tumor cells (lung cancer, breast cancer, and leukemia), intestinal epithelium, chondrocyte and neuron	embryonic development, tissue regeneration, inflammation, and tumorgenesis
IL-17C	IL-17RA/RE	keratinocytes, epithelial cells, dendritic cell, macrophages, and CD4+ T-cells	protection against pathogens and inflammation
IL-17D	Unknown	resting CD4+ T cells and resting CD19+ B cells	inhibition of hematopoiesis
IL-17E (IL-25)	IL-17RA/RB	T cells (GATA3+ (**Th2**), CD8+), mast cells, eosinophils, epithelial cells and endothelial cells	Th2 type immune response
IL-17F	IL-17RA/RC	T cells (Th17, Tc17) and innate lymphoid cells (ILC3)	protection against pathogens and inflammation

Bolded areas indicate important producing cells.

Table 1.
Overview of the Human IL-17 Family Members.

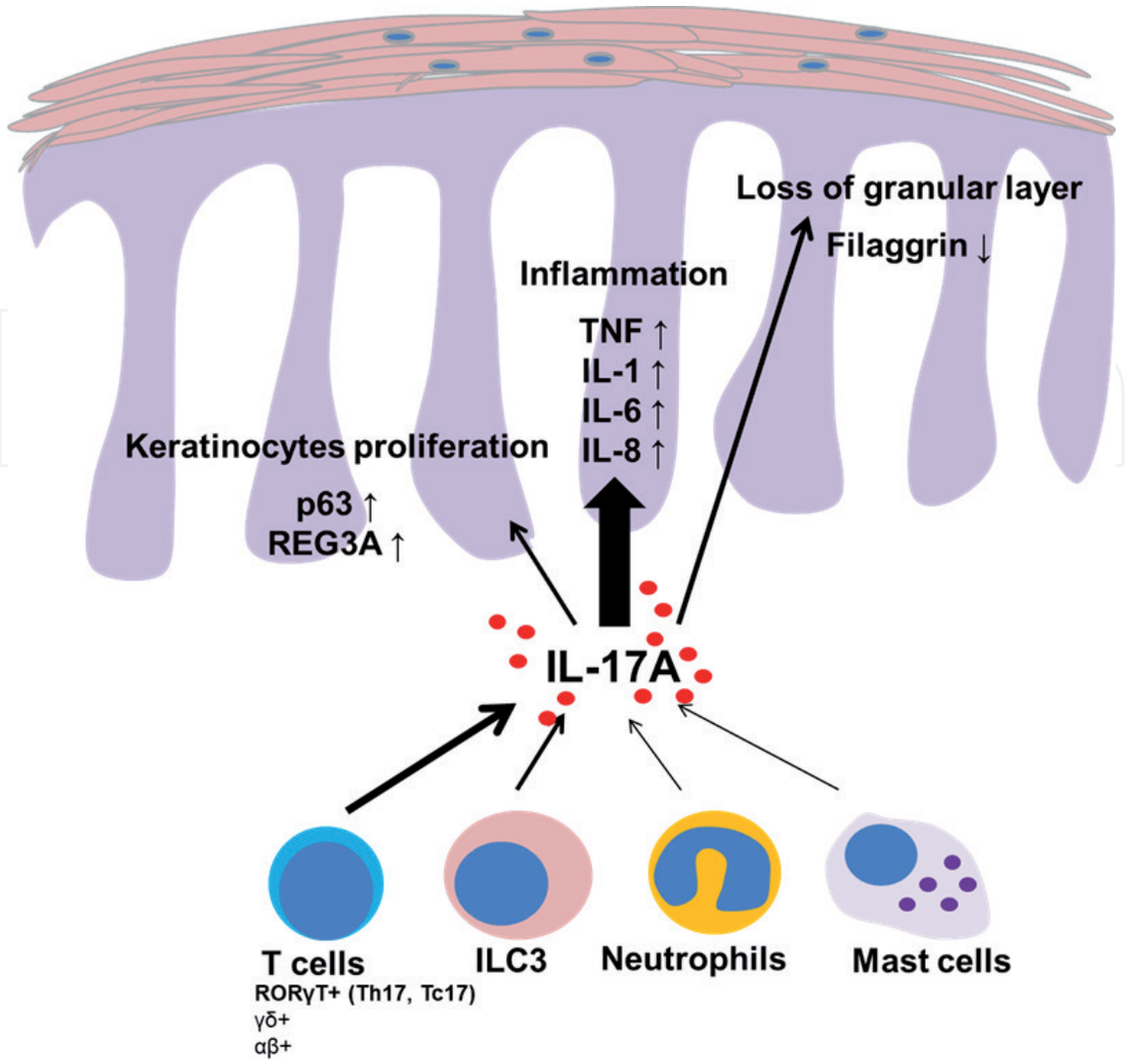


Figure 1.
The role of IL-17A in the skin. Immune cells, mainly Th17 cells, produce IL-17A, which promotes inflammation and proliferation of the epidermis, inhibits terminal differentiation, and causes loss of the granular layer.

2.2 IL-17B

Compared with IL-17A, IL-17B has not been studied as much, and so, its role remains unknown. IL-17B is the second most homologous to IL-17A, after IL-17F, but it is not produced by Th17 cells [25, 26]. In humans, IL-17B mRNA expression was confirmed in the tissues of the pancreas, small intestine, and stomach [27]. Although IL-17B did not induce a strong production of IL-6 directly from fibroblasts as IL-17A did, it did enhance the production of G-CSF and IL-6 in TNF-α-stimulated fibroblasts [27, 28]. However, there are reports that IL-17B has anti-inflammatory effects and is protective against asthma and colitis [29]. Recently, it was reported that IL-17B is positioned as a new component in the regulation of human type 2 immunity [30]. IL-17B has also been reported to promote the progression of malignant tumors such as lung cancer and breast cancer [31, 32]. The role of IL-17B on the epidermis is unknown and needs to be verified in the future.

2.3 IL-17C

IL-17C is known to be expressed by epithelial cells including keratinocytes, innate immune cells such as dendritic cells and macrophages, and CD4+ T-cells [19]. IL-17C stimulates Th17 T-cells to increase synthesis of IL-17A/F and IL-22,

and then IL-17A strongly induces IL-17C in keratinocytes, forming an inflammatory loop [33]. One study reported that overexpression of IL-17C in keratinocytes promotes psoriasiform skin inflammation in mouse experiments [34]. It has also been reported that neutralizing IL-17C suppressed atopic dermatitis and psoriasis-like dermatitis in mice [35]. IL-17C neutralizing antibody, MOR106, inhibits both Th2-type and Th17-type immune responses; and clinical trials for atopic dermatitis are being conducted against the IL-17C neutralizing antibody MOR106 [33, 36]. In a three-dimensional human epidermal model using normal human keratinocytes, nine genes, including S100A7A, were reported to be commonly upregulated by IL-17A and IL-17C, but IL-17A induced the loss of the granular layer in the epidermis, whereas IL-17C did not induce such epidermal changes [22]. Also, although IL-17A is protective against fungal infections, IL-17C deficiency is reported as lethal against systemic infection with Candida albicans by IL-17C deficient mouse model [37]. However, another study using IL-17C deficient mice reported that IL-17C is not involved in immunity against Candida infection [38]. In murine bacterial infection models, IL-17C has been shown to be protective against infection by Citrobacter rodentium, Pseudomonas aeruginosa, and Haemophilus influenzae [39–41]. In viral infections, ex vivo administration of IL-17C to mice reduced the apoptosis of neurons caused by HSV-2 infection, suggesting that keratinocyte-derived IL-17C acts to protect nerve fibers during HSV-2 reactivation in the skin [42]. It is also known that IL-17C is secreted through NF-κB activation by stimulation of pathogen-associated molecular patterns (PAMPs) [43] and is secreted in an autocrine manner to play a role in the initial defense response against pathogens [44, 45].

2.4 IL-17D

IL-17D has not been studied as much as IL-17A [46]. IL-17D was found to be highly expressed in the skeletal muscle, brain, adipose tissue, heart, lung, and pancreas, while low in the bone marrow, fetal liver, kidney, leukocyte, liver, lymph node, placenta, spleen, thymus, and tonsillar tissue [47]. IL-17D is also expressed at low levels on resting CD4+ T-cells and resting CD19+ B cells. IL-17D was poorly expressed on activated CD4+ T-cells, resting and activated CD8+ T-cells, resting and activated CD14+ monocytes, and activated CD19+ B cells. [47]. IL-17D, like other IL-17 family members, was capable of stimulating the production of other cytokines such as IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [48]. IL-17D stimulates human umbilical vein endothelial cells to produce IL-8 to levels in the physiological range that inhibit hematopoiesis [49]. However, it has also been reported that the level of GM-CSF produced by human umbilical vein endothelial cells is much lower than that required to stimulate myeloid proliferation [50]. The expression of IL-17D mRNA has been found to be decreased in psoriatic skin, but the reason for this is still unresolved [51].

2.5 IL-17E

IL-17E, also known as IL-25, has the lowest homology with IL-17A, among its other five family members [25, 26]. The most important difference between IL-17E and IL-17A is that IL-17E is involved in the Th2 type immune response [19]. On the other hand, IL-17E induces immune responses by IL-5 and IL-13 through ILC2 in a T cell-independent manner [52]. In autoimmune diseases, IL-17E has been thought to negatively regulate pathogenesis by suppressing Th17-type immune responses [53]. However, it was recently reported that IL-17E is highly expressed in the epidermis of imiquimod-induced psoriasis in mice, and that IL-17E promotes

keratinocyte proliferation and inflammatory responses, leading to psoriasis-like skin inflammation [54]. These two contradictory reports are both based on experiments using IL-17E deficient mice, but need to be validated in actual human psoriasis epidermis in the future.

2.6 IL-17F

IL-17F has the highest homology (40–55%) with IL-17A, followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (17%) [25, 26]. Like IL-17A, IL-17F binds to the IL-17RA/IL-17RC heterodimer receptor. Also, studies have known that IL-17F forms a homodimer or heterodimer with IL-17A when it binds to the receptor [55, 56]. As well as loss-of-function mutations in IL-17RA, it has been confirmed that partial loss-of-function mutations in IL-17F cause chronic mucocutaneous candidiasis [57]. IL-17F induces a variety of inflammatory molecules such as IL-6 and IL-8 via NF-κB, mitogen-activated protein kinase (MAPK), and CCAAT/ enhancer binding protein (C/EBP) [19]. IL-17F is derived primarily from Th17, Tc17, and ILC3 to enhance skin inflammation [58]. Bimekizumab (a biologic of both IL-17A and IL-17F) has been reported to be more effective than blocking IL-17A or IL-17F alone, particularly in inhibiting neutrophil chemotaxis and activation of synovial cells or human dermal fibroblasts in vitro [59].

3. What effect does IL-17 have on the epidermis?

3.1 Inflammation

IL-17A and IL-17F bind to IL-17RA/IL-17RC heterodimeric receptors and activate NF-κB, MAPK, and C/EBP, thereby inducing inflammation with cytokines such as IL-1, IL-6, and TNF-α and chemokines such as IL-8 (CXCL-8) and CXCL-1. These then activate neutrophils and cause migration to inflammatory sites [19, 60]. IL-17C is also known to activate NF-κB and MAPK pathways after binding to IL-17RA/IL-17RE receptors [36, 45]. IL-17C stimulates Th17 T-cells to increase synthesis of IL-17A/F and IL-22, and IL-17A strongly induces IL-17C in keratinocytes, forming an inflammatory loop [33]. IL-17E binds to IL-17RA/IL-17RB receptors and activates NF-κB, MAPK, and C/EBP, but differs from IL-17A in that it induces Th2-type immune responses and then suppresses Th-17 [53]. IL-17E promotes the migration of eosinophils, but not neutrophils [19].

3.2 Proliferation and differentiation

Mice overexpressing IL-17A in K14+ keratinocytes showed yellowish thickening of the epidermis, loss of the stratum granulosum, elongation of the dermal papillae, areas of hyperkeratosis and parakeratosis in the stratum corneum, and multiple neutrophilic abscesses, which are strikingly reminiscent of the epidermis of psoriasis [61]. In a three-dimensional epidermal model using normal human keratinocytes, IL-17A downregulated the expression of epidermal terminal differentiation markers such as filaggrin and loricrin after 5–6 days of incubation [22, 23] and caused the loss of the epidermal granular layer [22]. It has been reported that MAP17, whose expression is enhanced in normal human keratinocytes by IL-17A stimulation, downregulates mRNA expression of filaggrin [62]. On the other hand, there is a report that IL-17A did not downregulate mRNA of filaggrin and loricrin in the 3D epidermis 24 h after administration of IL-17A recombinant [63]. Similarly, in an experiment in which IL-17A recombinant was administered to confluent *in vitro*

keratinocytes transfected with control and *TRAF3IP2* shRNA-expressing lentiviruses, mRNA expression was confirmed 24 h after recombinant administration, and at this point, there was still no significant difference in the terminal differentiation marker genes [64]. What these papers have in common is that they confirmed the expression of terminal differentiation marker genes after a short period of IL-17A stimulation (24 h), which may have led to different data from those reported above [22, 23]. In fact, another paper using *in vitro* normal human keratinocytes showed that mRNA expression of keratin 10, an intermediate differentiation marker gene, was downregulated at 48 h after IL-17A stimulation [65]. They also showed in the same paper that IL-17A promoted keratinocyte proliferation as well as IL-22 [65]. There are several reports that IL-17A promotes epidermal proliferation as shown in this paper. In particular, it is known that asymmetric cell divisions predominate over symmetric cell divisions in the epidermis of psoriasis, and IL-17A was reported to cause asymmetric cell divisions in normal human keratinocytes [66]. It has been reported that the promotion of epidermal proliferation by IL-17A is mediated by C/EBPα [67]. Furthermore, regenerating islet-derived protein 3-alpha (REG3A) promotes proliferation by suppressing keratinocyte terminal differentiation after injury to the epidermis [68]. In an experiment using a three-dimensional human epidermis model, IL-17C had no specific effect on the final differentiation markers of the epidermis and did not cause granular layer loss [22]. However, there is a report that overexpression of IL-17C in K5+ keratinocytes promotes psoriasiform skin inflammation in mouse experiments [34]. IL-17E promoted keratinocyte proliferation and upregulated the expression of keratin 10 in two- and three-dimensional cultures [69].

3.3 Migration

IL-17A increased actin stress fibers, promoted cellular contractility, and increased proteolytic collagen degradation, resulting in the increased migration potential of normal human keratinocytes [70]. A431, an epidermoid carcinoma cell line, also showed similar findings, suggesting that IL-17A may promote the invasion of malignant skin tumors. There are also reports of IL-17E affecting cell migration. This was accompanied by specific changes in the organization of the actin cytoskeleton and cell-substrate adhesion [69].

3.4 Adhesion

In a study using HaCaT cells, microarray experiments showed that IL-17A decreased the expression of 16 adhesion-related genes, including various integrins, plakoglobin, plakophilin, cadherin (including E-cadherin), claudin 7, and ZO-2 protein [71]. However, studies using normal human keratinocytes have not clarified the down regulation of adhesion molecules, and this needs to be verified in the future.

4. Skin diseases in which IL-17 is clearly involved

4.1 Psoriasis

The mRNA expression of IL-17A, IL-17C, IL-17E, and IL-17F is upregulated in psoriatic skin [51, 54, 72]. However, the fact that anti-IL-17A antibodies resolve the psoriatic skin lesions indicates that IL-17A is the most important player in the pathogenesis of psoriasis [1–3]. IL-17A induces inflammation and is directly involved in

neutrophil migration and epidermal differentiation [19–22]. IL-17C stimulates Th17 T-cells to increase the synthesis of IL-17A/F and IL-22, and IL-17A strongly induces IL-17C in keratinocytes to form an inflammatory loop [33], but there are still insufficient human data indicating that IL-17C inhibition is effective in psoriasis. IL-17C may not be an essential component of IL-17A synthesis. In addition, there is no significant difference between the effects of IL-17RA antibodies (Brodalumab) and IL-17A antibodies (Ixekizumab and Secukinumab), which are the major receptors for IL-17A, IL-17E, and IL-17F. IL-17RA antibodies inhibit IL-17A and IL-17F signaling, but also block IL-17E signaling, so the possibility of offsetting Th17 suppression should be considered. If Bimekizumab, IL-17A/IL-17F antibodies, show greater efficacy than IL-17A in the future, the importance of IL-17F in psoriasis will be firmly established.

4.2 Hidradenitis suppurativa

The pathogenesis of Hidradenitis Suppurativa (HS) is still not fully understood [73]. HS is reported to be caused by follicular occlusion induced by keratosis and hyperplasia of the follicular epithelium, which eventually leads to the development of cysts [73, 74]. The occluded follicles eventually rupture, releasing their contents into the dermis, including keratin fibers, dermal detritus, multiple injuries, and pathogen-associated molecular patterns. Inflammatory immune pathways such as inflammasomes, Toll-like receptors, and IL-23/IL-17 signaling pathways are then activated [75]. The keratinocytes and innate immune cells activated will likely prompt a strong Th17 response, further activating the keratinocytes and recruiting neutrophils and other innate immune cells in an inflammatory loop. Th17 cells and neutrophils have been reported as the major IL-17-producing cells in the lesioned skin of HS [76, 77], and IL-17A gene expression in the lesioned skin of HS patients has been found to be 30- to 149-fold increased compared with healthy control skin [78, 79]. Recently, it has also been suggested that IL-17C may be involved in the pathogenesis of HS [80]. A variety of IL-17-related biologics are currently being investigated for HS, including CJM-112, secukinumab, bimekizumab, brodalumab, and guselkumab. Secukinumab treatment in HS has shown positive results in a series of case studies and open-label trials, with a Phase III trial underway [81, 82].

5. Conclusion

The effect of IL-17 on keratinocytes and the epidermis has a direct and significant impact not only on inflammation but also on epidermal differentiation. In particular, IL-17A has been the most studied, as clinical findings indicate that it is strongly involved in the pathogenesis of psoriasis and HS. However, other IL-17 family members have not been studied as extensively as IL-17A, and further basic research will provide new insights.

Conflict of interest

The authors declare no conflict of interest.

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