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Review

IL-17 and its role in inflammatory, autoimmune, and oncological skin diseases: state of art

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Abstract

Recent data support the theory of the involvement of IL-17 in the pathogenesis of several chronic inflammatory skin diseases (psoriasis, atopic dermatitis, acne, hidradenitis suppurativa) and autoimmune skin diseases (alopecia areata, vitiligo, bullous diseases). Even if the role of IL-17 in inflammatory and autoimmune diseases has been reported extensively, its role in tumor is still controversial. Some reports show that Th17 cells eradicate tumors, while others reveal that they promote the initiation and early growth of tumors. Herein, we review the role of IL-17 in the involvement of some common dermatologic diseases: psoriasis, atopic dermatitis, hidradenitis suppurativa, acne, vitiligo, melanoma, and nonmelanoma skin cancers.

Introduction

IL-17 is a cytokine whose family consists of six members, from IL-17A to IL-17F, even if the term IL-17 usually refers to IL-17A.[1] All the family members share some activities: IL-17A, IL-17F, and their heterodimers IL-17A/F have inflammatory effect with different strength; IL-17B, IL-17C, IL-17D are proinflammatory cytokines with unknown role. The IL-17E cytokine, also named IL-25, is involved in Th2 cells response.[2]

Production of IL-17 is mainly operated by T helper type 17 (Th17), $CD8^+$ T cells, $\gamma\delta$ T cells, invariant natural killer T cells (iNKT), natural killer (NK) cells, natural Th17 cells, and lymphoid tissue inducer (LTi) cells.[1]

IL-17 exerts many physiological functions including: neutrophil recruitment, Th2 stimulation to provide an effective response against extracellular organisms, macrophage production of IL-1β and TNF-α, and inflammatory mediator matrix metalloproteinases (MMPs) induction.[1]

[Correction added on March 05, 2020 after first online publication: the copyright line has been changed.]

Despite of the important role of IL-17 cytokine in regulating adaptive and innate immune systems,[3] its overproduction could be involved in several diseases.[4]

In recent years, different studies have tried to associate the IL-17 pathway to an increasing number of inflammatory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), lupus, polymyalgia rheumatica, giant cell arteritis, Behçet disease, dry-eye syndrome, Sjögren's syndrome, Crohn's disease, and multiple sclerosis. However, the role of IL-17 is still unclear.[4] Th17 cells and IL-17 have also been identified to be implicated in the pathogenesis of several human autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic sclerosis, primary Sjogren's syndrome, alopecia areata, and vitiligo.[5] Furthermore, a recent study reported a correlation between the serum levels of IL-17 and activity of the disease in selected autoimmune bullous skin diseases, such as dermatitis herpetiformis (DH), bullous pemphigoid (BP), and pemphigus vulgaris (PV).[6]

Even though the role of IL-17 in inflammatory and autoimmune diseases has been reported extensively, its role in tumors is still controversial.[7]

In an attempt to contribute to the description of the relationship between IL-17 pathways and the most frequent dermatological diseases, we report the state of the art about the role of IL-17 in psoriasis, atopic dermatitis, acne, hidradenitis suppurativa, vitiligo, alopecia areata, nonmelanoma skin cancer, and melanoma.

IL-17 and Inflammatory Skin Diseases

Psoriasis

Recent evidences highlighted the importance of IL-17A in the pathogenesis of psoriasis and psoriatic arthritis. IL-17A upregulates the expression of inflammation-related genes in keratinocytes and fibroblasts, resulting in the production of inflammatory cytokines, chemokines, and other mediators and the consequent clinical features.[8]

Linag *et al*. support the emergent role of IL-17 in psoriasis pathogenesis, proving its effects on keratinocyte cultures to increase the expression of antimicrobial peptides (e.g. S100) and chemokines (e.g. CCL20) that activate and recruit neutrophils and T cells.[9] Recent data reported a serum increase of IL-17 in psoriatic patients.[10] The IL-17 binding to its receptor (IL-17R) expressed by keratinocytes promotes the aberrant differentiation and proliferation of keratinocytes, the expression of chemokines (CXCL1, CXCL2, and CCL20) which enhance recruitment of Th17 and dendritic cells to the skin, the expression of antimicrobial peptides, and reduces the expression of cell adhesion molecules, resulting in disruption of skin barrier function.[11]

Zhang *et al*. in a recent work on a pediatric population reported a significantly higher frequency of Th17 and its cytokines in psoriatic patients' blood compared with healthy controls, pointing out a significantly positively relation between the increase of Th17 blood frequency and patient PASI.[12] Likewise, Sofen *et al*. and Chiricozzi *et al*. reported a significant correlation between IL-17 serum levels and disease severity, while Yilmaz *et al*. found an increase in IL-17 in serum of patients with PASI > 10 more than patients with PASI < 10.[13–15] Different authors have studied the correlation between serum levels of IL-17 or its tissue expression and the clinical subtype of psoriasis or disease state.[16,17] Recently, the central role of IL-17 in systemic inflammation and cardiovascular comorbidity in psoriasis patients has also been highlighted.[18–20]

Finally, the evidence of the role of IL-17 in the pathogenesis of psoriasis has been supported by the proven efficacy of the treatment with anti-IL-17 in psoriatic patients.[8,21,22]

In particular, the biological agent brodalumab proved its efficacy and safety in generalized pustular psoriasis.[23]

Atopic dermatitis

The central role of cytokines in the pathogenesis of atopic dermatitis (AD) has been widely highlighted. Interleukin-4 and interleukin-13 are major causes of inflammation and itch in patients.[24] Recently, the role of Th17 cells and IL-17 in the pathogenesis of AD has been investigated. Th17 cells play a potential role in the immune activation, including attraction of neutrophils.[25] An increase in IL-17A, IL-17E, IL-17F, and IL-23 serum concentrations has been demonstrated in children suffering from AD, which correlated with disease severity.[26] Elevated IL-17A and IL-17E levels were found in the papillary dermis of AD lesions, especially in the acute phase.[27] In AD mouse models, IL-17E is upregulated inducing the expression of endothelin-1, which is an important factor in developing pruritus.[28] IL-17E may be responsible for skewing the immune response to a Th2 dominance and decreases filaggrin production in keratinocytes, resulting in disorders of keratinization and an impaired skin barrier function/homeostasis.[29] Considering the role of IL-17 in the pathogenesis of DA, it is reasonable to speculate a possible effectiveness of anti-IL-17 in the treatment of AD. As anti-IL-17A therapy in psoriasis increases the risk of neutropenia and skin and oral candida infections, it seems reasonable to be cautious, as AD patients are more prone to skin and mucosal infections than patients suffering from psoriasis.[30]

Acne

The evidence of the presence of inflammatory factors in the very earliest stages of acne lesion prior to hyperproliferation of the follicular epithelium raises questions on the primary key role of inflammation in the pathogenesis of acne.[31]

Recently, the role of Th17 in acne lesions is under investigation. Examination of inflammatory changes in early acne lesions in two separate patient cohorts revealed a significant overexpression of cytokines involved in Th17 pathways.[32] Agak *et al*. confirmed these findings, demonstrating the ability of P. acnes in inducing both Th17 and Th1 responses as measured, respectively, by IL-17 and INF-ɤ in human peripheral blood mononuclear cells (PBMCs) *in vitro*, as well as the expression of Th17 differentiation markers including RORα, RORc, and IL-17RA and IL-17RC.[33] Moreover, at immunohistochemical examination, IL-17 expressing cells were detectable only in the epidermis of acne patients. $CD4^+CD25^+Foxp3^+$ regulatory T-cells (T-regs), a population linked to Th17 cells, are significantly increased in acne lesions. The differentiation of both Th17 cells and T-regs depends on the cytokines present in the environment.[34]

In a recent study, Kistowska *et al*. suggested that acne may be a Th17-mediated disease because P. acnes is a potent inducer of IL-17 and IFN-gamma from $CD4^+$ T cells and that $IL\text{-}17^+$ cells were present in perifollicular infiltrates in biopsy samples of inflammatory acne lesions.[35]

Another study has highlighted some therapeutic implications of the Th17 pathway in patients with acne.[36] Some drugs, such as dihydroxyvitamin D3, retinoids, vitamin A, and zinc, could have a successful role in the treatment of acne because of their inhibition of inflammatory Th17 and promotion of T-reg responses.[37]

Hidradenitis suppurativa

Recent research focused on the inflammatory mechanisms involved in HS, suggesting a key role for immune dysregulation

in its pathogenesis. Schlapbach *et al*. investigating the expression and cellular source of IL-12, IL-23, and IL-17 in lesional skin reported that IL-17 and IL-23, which play a central role in the regulation of Th17 cells, were highly expressed.[38] Van der Zee *et al*., comparing the cytokine levels in lesional HS skin biopsies after 24 hours of culture with the levels in healthy skin, showed that levels of IL-1β, TNF-α IL-6, and IL-17 were elevated in HS lesions.[39] Similarly, Kelly *et al*. reported that the mRNA expression of IL-17A, IL-1β, TNFα, and IL-10 is enhanced in lesional skin. In addition, they showed a significant enhancement of IL-17A in uninvolved skin of patients with HS 10 cm away from any lesional activity.[40] Based on these data, the abnormal expression of IL-17 and its associated cytokine detected in lesional skin and uninvolved skin supported the hypothetical role of Th17 in lesion development. Likewise, Lima *et al*. demonstrated that the Th17 cells and neutrophils are significantly increased in lesional and perilesional skin with homogeneous distribution in the perifollicular region.[41] The evidences supporting the role of IL-17 in the pathogenesis of HS provided a rationale for treating hidradenitis with anti-IL-17 antibodies, especially in case of HS refractory to local and systemic antibiotic therapy as well as other biological drugs.[42]

IL-17 and Autoimmune Skin Diseases

Vitiligo

Several human studies have investigated the roles that Th17 cells play in vitiligo, demonstrating an increased frequency of circulating Th17 cells and elevated serum levels of IL-17 that positively correlates with disease duration, extent, and severity of disease.[43]

In a recent study, Kotobuki *et al*. confirmed the presence of Th17 cell infiltration in vitiligo skin and speculated that Th17 cells do not exert a direct effect on the melanocytes but by producing cytokines.[44] Therefore, the presence of a cytokine network and the secretion of IL-17A from Th17 cells may represent a new mechanism underlying the pathogenesis of vitiligo.

Assessing the role of IL-17 in the pathogenesis of vitiligo, Bassiouny *et al*. demonstrated elevated IL-17 levels in lesional skin, while Basak *et al*. showed a positive correlation between serum IL-17 levels and the extent of the depigmentation area in vitiligo.[45,46]

Evaluating the frequencies of peripheral blood Th17 cells and serum levels of IL-17A and Th17 cell-related cytokines in 45 patients with NSV, Zhou *et al*. showed increased circulating Th17 cells as well as elevated serum IL-17A, TGF-β1, and IL-21 levels in NSV patients, suggesting their potential involvement in the development and progression of NSV.[47] These data supported the evidence that Th1 and Th17 played an important role in cellular immunity in the progression of vitiligo.

Further clinical studies are needed to confirm this correlation and to determine the implications of directly targeting the IL-17 pathway in order to treat vitiligo.

Alopecia areata

Recent evidences highlighted the role of both Th17 cells and T regulatory (Treg) cells in the pathogenesis of alopecia areata (AA).[48,49] Loh *et al*. carried out a study in order to determine whether AA is associated with alterations in lesional and serum Th17 and Treg cytokines. Studying scalp biopsies and serum samples from AA patients, they found out that lesional IL-17, IL-22, and serum IL-1, IL-17, TNF-α, and TGF-β were significantly higher in AA patients than in controls. Moreover, they demonstrated that there were positive correlations between lesional and serum IL-17 and disease severity.[48]

A similar result has been demonstrated recently in another study which found higher serum IL-17 level in patients with AA than in control subjects. In particular, El-Morsy *et al*. revealed significantly higher serum IL-17A levels in patients aged ≤30 years compared with those aged >30 years. This significant negative correlation between patient age and serum IL-17A was not detected in the control group.[49] With regard to the association among IL-17A levels and gender, age, disease duration, subtype, or number of patches, Atwa *et al*. found that the concentrations of IL-17 are associated with disease severity and are different according to the clinical phenotype being lowest in patients with only one patch of hair loss and highest in alopecia universalis/totalis.[50]

Tanemura *et al*., performing immunofluorescent study of alopecia lesions, detected a significant infiltration of $CD4^+$ $IL\text{-}17A^+$ Th17 cells in the dermis, particularly around hair follicles, suggesting the involvement of Th17 cells in the pathogenesis of AA.[51]

These results provide evidence on a functional role of TH17 and IL-17 in the pathogenesis of AA and highlighted the potential therapeutic role by targeting Th17 cytokines for the treatment of AA.

IL-17 and Oncological Skin Diseases

NMSC

Besides other features, Th17 cells are characterized by pro- or antitumorigenic properties depending on the stimuli of the microenviroment.[7] Some reports showed that Th17 cells eradicate tumors, while others revealed that they promote the initiation and early growth of tumors.[52] The microenvironment can exert inhibitory effects on malignant cells, but tumors can circumvent these inhibitory signals and use the surrounding cells for their own survival, causing growth, invasion, and metastasis. The generation of Th17 cells with different phenotypes in response to tumor microenvironment would explain the conflicting observations.[7]

One evident role of Th17 cells in tumor progression is their contribution to local inflammation. Cytokines produced by inflammatory Th17 cells stimulate inflammation-dependent tumor growth by promoting angiogenesis and by suppressing antitumor immunity.[53] Particularly regarding NMSC, Nardinocchi *et al*.

investigated the role of IL-17 and IL-22 in the growth and invasiveness of human skin basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC). They showed that both tumor types are infiltrated with a high number of IL-17$^+$ and IL-22$^+$ T lymphocytes. *In vitro* studies demonstrated that IL-17 increased the proliferation and migration of the BCC- and SCC-cell lines M77015 and CAL27. This study, demonstrating a pro tumorigenic role of IL-17 in human SCCs and BCCs, suggested treatment with anti-IL-17 antibodies as a therapeutic approach in selected cases.[54]

In addition, an Italian group investigated changes of expression of IFN-γ, IL-17, IL-23, and IL-22 cytokines in BCC and their modulation during imiquimod (IMQ) treatment or photodynamic therapy (PDT). Increased levels of IFN-γ, IL-17, IL-23, and IL-22 were found in BCCs compared to normal skin, and their expression results correlated with the severity of the inflammatory infiltrate. Moreover, IL-17 was increased in nodular forms. Finally, they highlighted an increase of IFN-γ, IL-23, and IL-22, IL-17 because of early inflammatory response induced by IMQ and PDT treatment.[55]

These findings confirm the role of Th17 and related cytokines in NMSC pathogenesis and in the inflammatory response during therapies.

Melanoma

The role of Th17 and IL-17 in melanoma is complex, as it has been reported in NMSC. Effects of Th17 and IL-17 in murine models of cancer has been investigated, showing that Th17 cells activate endogenous cytotoxic CD8$^+$ T cells and eradicate melanoma in mice.[56] Muranski *et al*. reported that Th17-polarized cells better mediated destruction of advanced B16 melanoma, and their therapeutic effect was critically dependent on interferon (IFN) production.[57] In murine B16 melanoma, it has been shown that the tumor-promoting role of IL-17 has a direct effect on tumor cells through an IL-6-Stat3 signaling pathway.[58]

Recently, Jun Li *et al*. demonstrated that IL-7/IL-7R-Stat3-IL-17 pathway promotes melanoma growth, and its inhibition may contribute to tumor growth in murine models of melanoma.[59]

Based on these evidences, Ganzetti *et al*. have speculated that this model could be reproducible in human cutaneous melanoma. They studied the expression of interleukin-17 (IL-17), IL-23, and p73 in 35 malignant melanomas comparing them with benign melanocytic nevi and Spitz nevi. Their results showed a greater IL-17 and IL-23 immunohistochemistry expression in the melanoma group than in ordinary benign nevi.[60] These results could suggest a possible IL-17, IL-23, and p73 involvement in cutaneous melanomas with a hypothetical impact on melanoma invasiveness.

It has been hypothesized that IL-17 may stimulate cancer cells to produce some angiogenic factors (VEGF), thereby enhancing tumor angiogenesis.[58] These results could suggest a direct impact on the biological behavior of tumor cells in the local microenvironment and could explain the increased expression of VEGF and angiogenesis in invasive melanomas.

In patients with advanced inoperable melanoma, a better understanding of the regulation of cytokine and cellular immune activity in response to melanoma may be important in order to predict therapeutic response to immunotherapy, including treatment with ipilimumab. A recent study showed that in patients with regionally advanced melanoma enrolled in a trial of neoadjuvant therapy with ipilimumab at 10 mg/kg, baseline IL-17 level was significantly associated with the risk of subsequent development of severe immune-mediated diarrhea/colitis.[61] Further investigation and confirmation in larger trials is necessary in order to confirm these findings.

Conclusion

We reported a global up-to-date overview about the role of IL-17 in inflammatory, autoimmune, and oncological skin diseases. The literature data suggest that this cytokine has been implicated in these diseases with different pathways. It could be hypothesized that IL-17 might represent a link between different diseases underlying a common pathogenic basis where inflammation could be considered the distinctive benchmark and this cytokine as a marker. Further clinical studies are needed to confirm this correlation and to determine its implications for the development of new therapeutic approaches as well as the monitoring of disease activity and therapeutic response.

Questions (answers provided after references)

True/False

1 All the family members of IL-17 family have an inflammatory effect.
2 The pathogenetic mechanisms triggered by the binding of IL-17 with its receptor in patients with psoriasis result in disruption of skin barrier function.
3 There is no evidence about the efficacy of treatment with anti-IL-17 in psoriatic patients.
4 Psoriatic patients are more prone to skin and mucosal infections than patients suffering from atopic dermatitis.
5 Some drugs, such as dihydroxyvitamin D3, retinoids, vitamin A, and zinc, have a successful role in the treatment of acne because of their inhibition of inflammatory Th17.
6 In the case of HS refractory to antibiotic therapy or other biological drugs, there is evidence that supports the role of IL-17 in the pathogenesis of HS and provides a rationale for treating hidradenitis with anti-IL-17.
7 In a recent study, is it confirmed that Th17 cells exert a direct effect on melanocytes.
8 Is it demonstrated that the concentrations of IL-17 are associated with disease severity and are different according to the clinical phenotype.

9 Th17 cells are characterized by pro- or anti-tumorigenic properties depending on the stimuli of the microenvironment.

10 Better understanding of the regulation of IL-17 and cellular immune activity in response to melanoma to predict therapeutic response to immunotherapy could be an advantage for patients with advanced inoperable melanoma.

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Answers to questions

1 True
2 True
3 False
4 False
5 True
6 True
7 False
8 True
9 True
10 True