The role of interleukin-17 in the pathogenesis of hidradenitis suppurativa

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Abstract:

Hidradenitis suppurativa is a chronic inflammatory skin condition affecting primarily the axillary, perianal, and inguinal areas. Patients with hidradenitis suppurativa present with occlusion and subsequent rupture of follicular ducts, profound abscesses, fistulae, odorous discharge, fibrosis, and scar formation, causing significant morbidity. Knowledge of the pathogenesis of hidradenitis suppurativa is limited and treatment with antimicrobial drugs, immunosuppressants, and surgical procedures have shown varying results. The pathogenic role of the interleukin-17 cytokine family in chronic inflammatory skin conditions has been described. Interleukin-17A and interleukin-17F have similar properties and induce the production of cytokines, chemokines, antimicrobial peptides, and metalloproteinases, all of which take part in the inflammatory response. The efficacy of anti-interleukin-17A therapy in psoriasis has also been proven and anti- interleukin-17A drugs are already in use for this condition. There is currently no consensus on the role of interleukin-17 in the pathogenesis of hidradenitis suppurativa. Studies have demonstrated increased interleukin-17 mRNA expression in lesional hidradenitis suppurativa skin, whereas the protein concentrations of interleukin-17 were found to be normal compared to healthy control skin in one other study. A phase II clinical trial on anti- interleukin-17 therapy in hidradenitis suppurativa is ongoing.

Keywords: hidradenitis suppurativa, interleukin-17

Introduction:

Hidradenitis suppurativa is a chronic inflammatory skin condition affecting primarily the axillary, perianal, and inguinal areas of the body. Hidradenitis suppurativa is characterized by initial occlusion and subsequent rupture of follicular ducts leading to formation of profound abscesses (**Figure 1**). Fistulae, odorous discharge, fibrosis, and scar formation are seen in later and more severe stages of hidradenitis suppurativa (**Figures 2, 3**). Onset of hidradenitis suppurativa is typically post pubertal, in the second to third decades of life.

The prevalence of hidradenitis suppurativa in the French population is estimated to be around 1%, although other studies have estimated prevalence rates ranging from as low as 0.0033% to as high

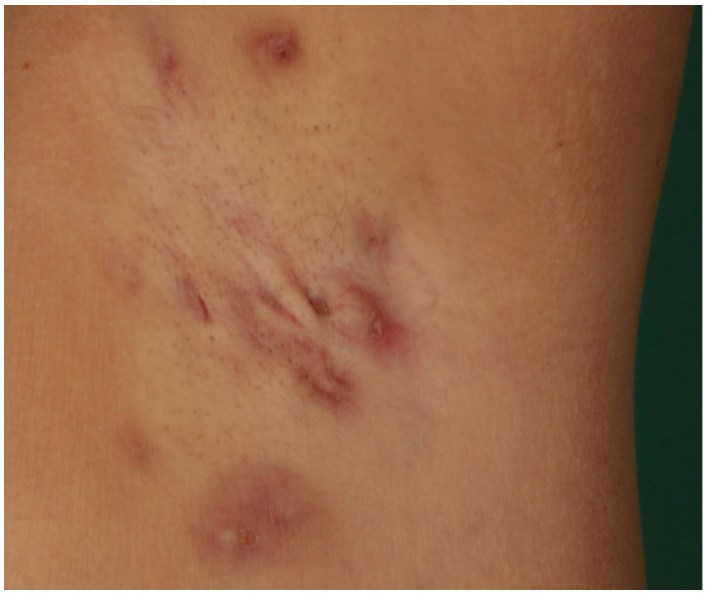

Figure 1. *Abscess formation and inflammatory nodules in hidradenitis suppurativa.*

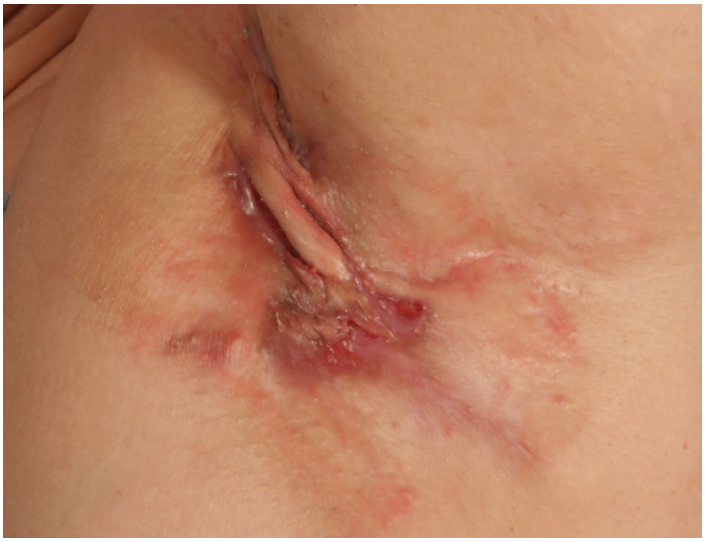

Figure 2. *Fistula formation with rope-like scar in hidradenitis suppurativa.*

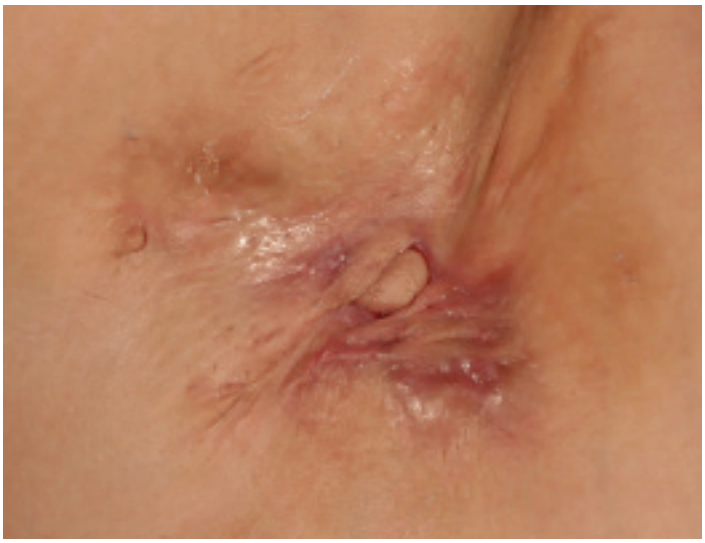

Figure 3. *Sinus tract and scar formation in hidradenitis suppurativa.*

as 4% in the general population [1-4]. Up to 40% of hidradenitis suppurativa cases have a positive family history and a dominant genetic inheritance pattern has been suggested. Smoking might be a direct risk factor for the development of hidradenitis suppurativa. Although overweight status is not considered a direct risk factor, overweight and obese patients present with significantly more severe disease [5]. Patients with hidradenitis suppurativa have a significant reduction in quality of life that exceeds that of other common skin diseases such as psoriasis and atopic dermatitis [2].

Treatments of hidradenitis suppurativa include: surgical procedures such as laser treatment and excision, medical treatments with topical and systemic medications, and adjuvant treatments for pain and absorption of drainage fluid. Commonly used topical preparations include azelaic acid and clindamycin. Effective systemic medications include tetracyclines, clindamycin plus rifampicin, acitretin, and anti-tumor necrosis factor biologics, preferably adalimumab and infliximab [6].

Clinical scoring systems for hidradenitis suppurativa

Several scoring systems to describe the severity of hidradenitis suppurativa exist but the most commonly used is the Hurley staging classification system. Hurley stage I corresponds to: solitary or multiple isolated abscesses without scarring or sinus tracts. Hurley stage II corresponds to: recurrent abscesses, single or multiple widely separated lesions with sinus tracts and scarring. Hurley stage III corresponds to: diffuse involvement across a regional area with multiple interconnected sinus tracts, abscesses, and scarring, [5], (**Table 1**).

Whereas the Hurley staging system only has three categories and only accounts for the clinical presentation, other more advanced systems exist to categorize treatment effectiveness and quality of life impairment. In 2003 Sartorius et al. proposed four parameters in the evaluation of treatment effectiveness (Hidradenitis Suppurativa Score): 1) anatomical region involvement; 2) number of lesions (abscesses/nodules and fistulae); 3) longest distance between two relevant lesions; and 4) clear separation of all lesions by normal skin [7]. A final numerical score is constructed from the analysis of each of these parameters for each anatomical region (axillae, groin, buttocks), with higher scores correlating with higher disease intensity. With this numerical and dynamic Hidradenitis Suppurativa Score, disease intensity can be specified and quantified, and the development of the disease can be measured before and after treatment. The Hidradenitis Suppurativa Score has been shown to correlate significantly with smoking and higher body mass index [8]. The Hidradenitis Suppurativa Clinical Response (**Table 1**) is another score that has been developed for use in clinical trials as it mirrors a clinically meaningful effect of treatment [9].

Table 1. Scoring systems for hidradenitis suppurativa.

Hurley stages	
Stage I	Solitary or multiple isolated abscess formation without scarring or sinus tracts
Stage II	Recurrent abscesses; single or multiple widely separated lesions with sinus tracts and scarring
Stage III	Diffuse involvement across a regional area with multiple interconnected sinus tracts, abscesses and scarring
Hidradenitis Suppurativa Severity Score System (HS4)	
Mild	a) 1 anatomical region OR ≤4 active inflammatory lesions (nodules or abscesses) OR b) Dermatology Life Quality Index <10 points
Moderate	a) 2 or more anatomical regions OR 5-9 active inflammatory lesions (nodules, abscesses or sinus tracts) OR b) DLQI Dermatology Life Quality Index 10-19 points
Severe	a) 2 or more anatomical regions AND ≥10 active inflammatory lesions (nodules, abscesses or sinus tracts) OR b) DLQI Dermatology Life Quality Index ≥20 points
Hidradenitis Suppurativa Clinical Response (HiSCR)	
HiSCR-50 corresponds to	a) ≥50% reduction in inflammatory lesion count (nodules and abscesses) AND b) No increase in abscess count AND c) No increase in draining fistula count
Hidradenitis Suppurativa Score (Sartorius)	
Composite score of	a) Anatomical region involved (left and right side: axilla, groin, gluteal, or other region), 3 points per region

The Hurley and Hidradenitis Suppurativa Score systems are but objective measures of disease severity and therefore, subjective scoring systems are needed to fully assess the patient-specific impact of the disease. Using various skin-specific and generic quality of life measures studies have

shown that patients with hidradenitis suppurativa have significantly reduced quality of life exceeding that of acne, psoriasis, atopic dermatitis, and neurofibromatosis 1 [10, 11]. The Hidradenitis Suppurativa Severity Score System [12], (**Table 1**), the Acne Inversa Severity Index [13] and the Hidradenitis Suppurativa Severity Index [14] combine objective measures with quality of life of the patients.

Association of IL-17 with hidradenitis suppurativa

Interleukin-17A, commonly referred to as interleukin-17, is a member of the interleukin-17 cytokine family alongside interleukin-17F. These factors stimulate the production of multiple chemokines with the majority being chemokine CXC ligand 1, chemokine CXC ligand 8, and chemokine CC ligand 20 [15-17]. Collectively these molecules serve to recruit neutrophils, macrophages, and lymphocytes to sites of inflammation. T helper 17 cells, the main producers of interleukin-17, express chemokine receptor 6 themselves, the receptor for chemokine CC ligand 20, thereby facilitating homing to the inflammatory sites and amplifying the immune response [18]. Furthermore, interleukin-17 induces the production of interleukin-1β and interleukin-6 in macrophages [17], interleukins crucial for the development of T helper 17 cells, augmentation of cell differentiation, and subsequent increase in interleukin-17 production.

Several chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and acne have already been linked to the inflammatory effects of interleukin-17 [19]. Even though there are numerous comprehensive reviews and clinical studies on hidradenitis suppurativa, isolated studies on the role of interleukin-17 in hidradenitis suppurativa pathogenesis are scarce, and thus the topic remains to be elucidated.

In 2010, Schlapbach et al. [20] demonstrated a 30-fold increase in interleukin-17A gene expression in lesional hidradenitis suppurativa skin compared with normal skin by real-time polymerase chain reaction analysis. Recently, Kelly et al. [21] similarly demonstrated an impressive 149-fold increase in interleukin-17 mRNA expression in lesional hidradenitis suppurativa skin versus normal skin through the same method. Asymptomatic, perilesional skin had a 50-fold increase in interleukin-17 gene expression. Importantly, the presence of such large amounts of interleukin-17 mRNA in perilesional skin suggests a pathogenic function because inflammatory responses, although subclinical, were seen prior to the formation of active lesions (**Table 2**).

Additional evidence of the association of interleukin-17 with hidradenitis suppurativa was demonstrated by Wolk and coworkers in 2010 [1]. Their investigation of interleukin-22 deficiency in hidradenitis suppurativa identified interleukin-17 as an inducer of beta-defensin-2, an over expressed antimicrobial peptide found in hidradenitis suppurativa skin along with S100 calcium-binding protein A7. Adenosine monophosphates are crucial for the restriction of cutaneous infections. Simultaneously, they possess immunomodulatory and chemo-attractive properties, and could

Table 2. Interleukin mRNA expression and protein concentration data results from lesional hidradenitis suppurativa skin from different studies.

Study	Interleukin-17 mRNA expression	Interleukin-17 protein concentration
Wolk et al., 2010 [1]	Elevated	Not tested
Schlapbach et al., 2011 [20]	Elevated	Not tested
Kelly et al., 2015 [21]	Elevated	Not tested
Blok et al., 2016 [24]	Not tested	Not elevated

Protein concentrations were analyzed by enzyme linked immunosorbent assay, while mRNA expressions were analyzed by polymerase chain reaction.

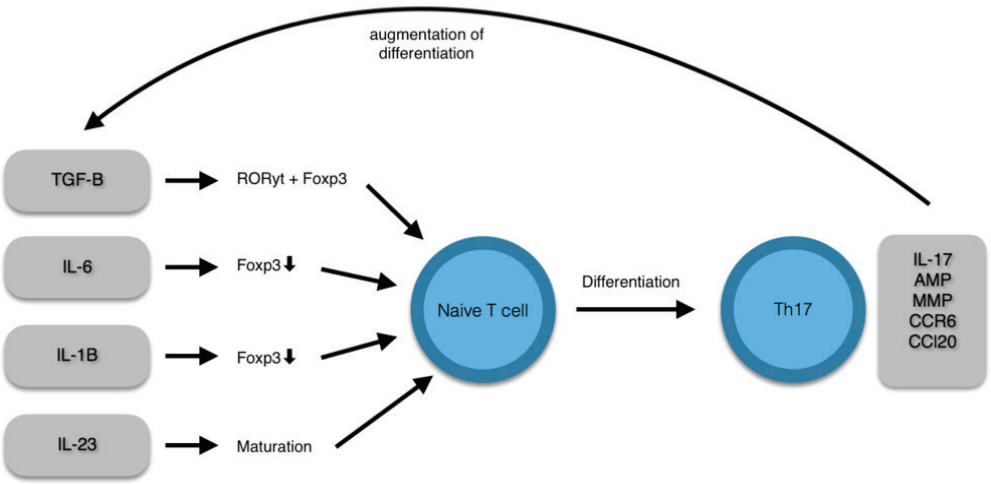

Figure 4. *Differentiation of T helper 17 cells in humans. Note: The four key cytokines transforming growth factor-β, interleukin-6, interleukin-1β, and interleukin-23 exert their functions on naive T cells, leading to a fully differentiated T helper 17 cell with the ability to secrete interleukin-17 as well as other effector molecules. Moreover, the secreted interleukin-17 potentates T helper 17 cell differentiation by enhancing the production of the differentiation factors required, thus creating a positive feedback loop.*

therefore, in concert with interleukin-17 induce chemokines, explain the histological changes of hidradenitis suppurativa characterized by infiltration of neutrophils, macrophages, and lymphocytes.

Transforming growth factor-*β*, interleukin-1*β*, interleukin-6 and interleukin-23 are well documented mediators of T helper 17 cell differentiation, each playing different roles in the process. Peripherally in naive T cells, transforming growth factor-*β* induces RAR-related orphan receptor gamma-γt, a transcription factor necessary for the generation of the T helper 17 cell lineage. Interleukin-6 down regulates Foxp3, a transcription factor, which generates regulatory T cells [15, 18, 23]. Interleukin-1*β* is produced by monocytes and macrophages and down regulates Foxp3 independently of interleukin-6 [15]. Interleukin-23 is a heterodimer consisting of an interleukin-12/interleukin-23 common p40 subunit and an interleukin-23 specific p19 subunit; it plays a role in the final maturation of T helper 17 cells [15], (**Figure 4**).

Of clinical importance, dendritic cells residing in the skin (Langerhans cells) are able to produce interleukin-1*β*, interleukin-6, and interleukin-23. Dendritic cells are also antigen presenting cells. In comparison to the differentiation of T helper 1/T helper 2 cell lineages, which require second signals in the form of costimulators interferon-*β* or interleukin-4, respectively, produced by other cell types (**Figure 5**), T helper 17 cell differentiation and activation only require one cell type because dendritic cells simultaneously present antigens and provide the critical differentiation factors [6]. Additionally, the locally produced interleukins in the dermis could play a role in the anatomical restriction of the inflammation seen in hidradenitis suppurativa, and at the same time explain why serum levels of these interleukins are not elevated [24].

Clinical relevance of interleukin-17 in skin diseases associated with hidradenitis suppurativa

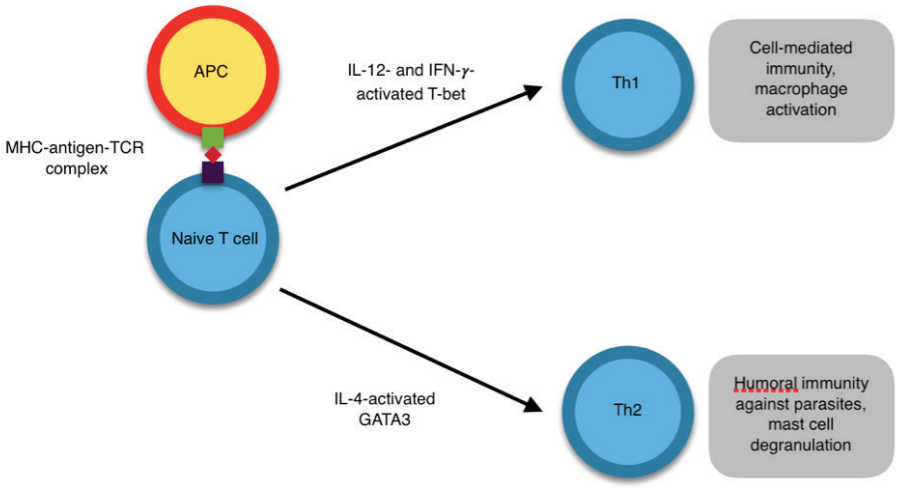

Figure 5. *T cell differentiation pathway. Note: T helper 1 differentiation is driven by a combination of interleukin-12 and interferon-γ. While interleukin 12 is innately produced by dendritic cells, interferon-γ is produced by natural killer cells. T helper 2 differentiation is stimulated primarily by interleukin-4, which is produced by the T cells themselves or mast cells activated by helminths or antigens/allergens. In both cases, the cell differentiation could require more than one cell type.*

The involvement of interleukin-17 is documented in the pathogenesis of psoriasis. Interleukin-17 and IL-23 mRNA expression was found to be elevated in psoriatic skin compared with normal skin, whereas T helper 17 cell counts in peripheral blood were increased three times.

One distinctive difference between the results of psoriatic and hidradenitis suppurativa skin analysis is in interleukin-22 mRNA expression. Although there was a deficiency of interleukin-22 in hidradenitis suppurativa, the opposite was true for psoriasis [16]. The ability of nterleukin-22 to induce adenoside monophosphates and strongly stimulate proliferation of keratinocytes is in agreement with the clinical presentation of psoriasis. Interleukin-17 and interleukin-22 synergistically induce high concentrations of adenoside monophosphates and keratinocyte proliferation, leading to the thick, dry, and scaly epidermis with very few and transient infections.

Targeting the interleukin-23/interleukin-17 axis is highly effective in treatment of plaque psoriasis [25]. Secukinumab, a monoclonal antibody specifically targeting interleukin-17A, was the first anti-interleukin-17A drug to be approved for the treatment of psoriasis by the Food and Drug Administration and the European Medicines Agency. More recently, the Food and Drug Administration has approved ixekizumab, another anti-interleukin-17A drug, and brodalumab, an interleukin-17 receptor antagonist. In clinical studies, 71% of patients achieved a psoriasis area and severity index 90 response after 12 weeks of treatment. Treatment with brodalumab has shown similar results with psoriasis area and severity index 90 response in 30 out of 40 patients after 12 weeks of treatment.

The anti-p40 drug, ustekinumab, which binds to the p40 subunit common to interleukin-12 and interleukin-23, has also shown considerable improvements in patients with psoriasis and psoriatic arthritis and is currently used for the treatment of these diseases. Similarly, ustekinumab has also shown efficacy in treatment of hidradenitis suppurativa [24]. Interleukin-23 specific drugs targeting only the p19 subunit are also in development.

Acne is another disease highly linked to hidradenitis suppurativa. A comprehensive study of the interleukin-17/T helper 17 cell pathway in acne lesions was published in 2014 [19]. The study comprised material from two independent clinical centers in Oulu, Finland and Berlin, Germany. Real time polymerase chain reaction analysis of gene expression in affected acne skin showed increased expression of interleukin-1β, interleukin-23, interleukin-6, and transforming growth factor-β, all involved in T helper 17 cell differentiation. In addition, increased expression of T helper 17 cell products, interleukin-17, and the chemokine CC ligand 20 was identified. Interleukin-17 producing cells, mainly lymphocytes but also neutrophils and mast cells, were detected in papillary dermis and around sebaceous follicles. Additionally, numerous adenoside monophosphates were also increased, including β-defensin-2 and S100 calcium-binding protein A7.

Ultimately, the study proposed that the follicular hyperkeratinization, increased expression of adenoside monophosphates, and accumulation of neutrophils in active acne lesions could partially be explained by the interleukin-23/interleukin-17 axis. Investigational trials of interleukin-IL-17 therapy in acne are ongoing.

Conclusion and future perspectives

As suggested by the studies presented herein, interleukin-17 plays a role in several chronic inflammatory skin conditions including hidradenitis suppurativa. The background knowledge on the proinflammatory properties of interleukin-17 combined with the studies revealing enhanced interleukin-17 gene expression in hidradenitis suppurativa patients provides a reason for the therapeutic value of targeting interleukin-17 and its receptors in the treatment of hidradenitis suppurativa. Currently, a phase II anti-interleukin-17 clinical trial in hidradenitis suppurativa is ongoing (ClinicalTrials.gov - identifier: NCT02421172). As the remaining functions of interleukin-17, along with the missing links in the pathogenesis of hidradenitis suppurativa are unveiled, the future looks promising for anti-interleukin-17 therapy in hidradenitis suppurativa. Nonetheless, further research is needed to clarify the role of interleukin-17 in the pathogenesis of

hidradenitis suppurativa.

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