SCHOLARLY REVIEW

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Aetiology and pathogenesis of hidradenitis suppurativa

K. Wolk,[1] O. Join-Lambert[2,3] and R. Sabat[4,5]

[1]Berlin-Brandenburg Centre for Regenerative Therapies, Charité–Universitätsmedizin Berlin, Berlin, Germany
[2]Groupe de Recherche sur l'Adaptation Microbienne (GRAM 2.0, EA 2656), Normandie University, UNICAEN, UNIROUEN, Caen, France
[3]Department of Microbiology, CHU de Caen Normandie, Caen, France
[4]Interdisciplinary Group of Molecular Immunopathology, Dermatology/Medical Immunology, Charité–Universitätsmedizin Berlin, Berlin, Germany
[5]Psoriasis Research and Treatment Centre, Charité–Universitätsmedizin Berlin, Berlin, Germany

Summary

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder. Patients develop inflamed nodules and abscesses and, at later stages of disease, epithelialized tunnels and scars in skinfolds of axillary, inguinal, gluteal and perianal areas. Quality of life is affected due to severe pain, purulent secretion, restricted mobility and systemic involvement. Genetics and lifestyle factors including smoking and obesity contribute to the development of HS. These factors lead to microbiome alteration, subclinical inflammation around the terminal hair follicles, and infundibular hyperkeratosis, resulting in plugging and rupture of the follicles. Cell-damage-associated molecules and propagating bacteria trigger inflammation and lead to massive immune cell infiltration that clinically manifests as inflamed nodules and abscesses. The immune system plays a key role also in the progression and chronification of skin alterations. Innate proinflammatory cytokines (e.g. interleukin-1β and tumour necrosis factor-α), mediators of activated T helper (Th)1 and Th17 cells (e.g. interleukin-17 and interferon-γ), and effector mechanisms of neutrophilic granulocytes, macrophages and plasma cells are involved. Simultaneously, skin lesions contain anti-inflammatory mediators (e.g. interleukin-10) and show limited activity of Th22 and regulatory T cells. The inflammatory vicious circle finally results in pain, purulence, tissue destruction and scarring. Chronic inflammation in patients with HS is also frequently detected in organs other than the skin, as indicated by their comorbidities. All these aspects represent a challenge for the development of therapeutic approaches, which are urgently needed for this debilitating disease. This scholarly review focuses on the causes and pathogenetic mechanisms of HS and the potential therapeutic value of this knowledge.

Correspondence
Robert Sabat.
Email: robert.sabat@charite.de

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Hidradenitis suppurativa (HS),[1] also known as acne inversa, is an inflammatory disorder affecting about 1% of the general population (discussed in a parallel scholarly review). The disease manifests in skinfolds of mostly axillary, inguinal, gluteal and perianal body areas. Starting around hair follicles, inflammation evolves into painful nodules, abscesses and, at a later stage, pus-discharging tunnels (sinus tracts or fistulas) and extensive scars. In patients with HS, inflammation is also frequently detected in internal organs, as reflected by the frequent association with metabolic syndrome, arteriosclerosis, spondyloarthritis and spondyloarthropathy, and inflammatory bowel disease.[2–5] Due to severe pain, purulent secretion, limitations in patients' mobility, and systemic involvement, HS has a profoundly negative influence on the quality of life of patients (discussed in a parallel scholarly review).[6] Furthermore, the metabolic and cardiovascular alterations contribute to the substantially reduced life expectancy of patients with HS.[7]

Despite the high burden on patients, the therapeutic options for HS are currently limited.[1] In order to improve that, a profound understanding of the aetiology and pathogenesis of HS is necessary. Our current understanding of the disease mechanisms is incomplete and largely based on descriptive data of HS lesions. In contrast, *ex vivo* mechanistic investigations and comparative studies involving other diseases are rare. The comparison with other cutaneous inflammatory disorders appears very relevant to the authors in terms of the estimation of the extent and the specificity of molecular and immunological alterations detected in HS. Clinical studies targeting selected immune mediators could deliver the ultimate proof of the pathogenetic relevance of specific molecules.

The following sections are devoted to the disease-predisposing factors, the pathogenetic processes, and the presentation of pathogenetic mediators. Our review did not aim to discuss every published article on the subject, but rather we have selected the most important ones, in our opinion.

Predisposing factors

Genetic factors

The importance of the genetic background was first noticed when Fitzsimmons and Guilbert observed disease clustering in 14 of 23 patient families.[8] In fact, around 30% of the patients reported a positive family history for HS.[9] A very limited number of patients with mostly severe HS disease with associated severe acne bear mutations in genes encoding the subunits of γ-secretase (γ-S),[10] a protease situated in the cell membrane.[11] Thirty-six different γ-S mutations have been described in HS, most of them in the gene for the nicastrin subunit.[12] The link between γ-S impairment and HS is supported by skin alterations that arise in young mice with genetic deficiency of γ-S components. In these mice, hair follicle disintegration and impaired sebaceous gland formation led to epidermal cyst development.[13] Interestingly, this occurred without relevant inflammation. When growing older, these mice developed squamous cell carcinomas.[13,14] Furthermore, therapeutic targeting of γ-S outside the dermatology field provoked follicular alterations and cyst formation in intertriginous skin areas.[15] Respective mutations in human γ-S may lead to hyperproliferation of keratinocytes.[16]

The long list of γ-S substrates includes amyloid-β protein precursor, interleukin (IL)-1 receptor 1, interferon (IFN)-αR2, CXCL16, RAGE and notch 1–4·[11] Interestingly, mice deficient in notch or notch ligand show a skin phenotype similar to that of γ-S mice.[13,17] The cleavage and consequent activation of notch are crucial for the development and homeostatic cycling of hair follicles.[18] Moreover, notch signalling is crucial for the function of regulatory T cells and IL-22 production by effector T cells,[19,20] which are both impaired in HS.[21] As described above, the prevalence of γ-S mutations among patients with HS is very low.[10] Moreover, it has not been proven so far that γ-S mutations in HS lead to notch deficiency.

Beside γ-S mutations, variations in further genes were identified in patients with HS.[22,23] One of these genes (*MEFV*) encodes the pattern-recognition receptor (PRR) pyrin,[23] a critical component of the inflammasome system. Activation of the inflammasome leads to production of IL-1β, a cytokine with an important role in HS pathogenesis (see below).

However, extensive studies are needed to investigate which genetic features contribute to the development of the disease in the majority of patients with HS with a positive family history. Several efforts including genome-wide association studies are under way.[23,24]

Lifestyle factors

There are two major lifestyle factors that, although not present in every individual patient, have accepted roles in HS disease development: obesity and tobacco smoking.

Central obesity has been found in approximately 60% of patients.[2] It is one of the factors defining the metabolic syndrome, a combination of medical conditions including central obesity, hyperglycaemia, dyslipidaemia and/or hypertension.[25] Approximately 40% of patients with HS have metabolic syndrome.[2] Investigating more than 400 hospitalized patients, Shalom *et al.* found that of the different metabolic syndrome components, obesity preceded the diagnosis of HS by an average of 5 years.[26] In line with this, central obesity had the highest frequency among metabolic syndrome criteria.[2] Importantly, there was a 4·5-fold increased risk of recurrence of skin alterations after laser-based surgical removal of skin lesions in obese vs. nonobese patients with HS.[27]

Obesity is supposed to favour HS skin alteration in two ways (Figure 1). Firstly, it enlarges the skinfolds in the body and, consequently, increases the mechanical stress, maceration and anaerobic conditions within those folds (see below). Secondly, it induces a low level of systemic inflammation and metabolic changes in respective individuals. In fact, inflammatory cells present in the hypertrophic adipose tissue produce proinflammatory cytokines and induce a dysregulated pattern of adipokines, all of which may have negative effects on skin

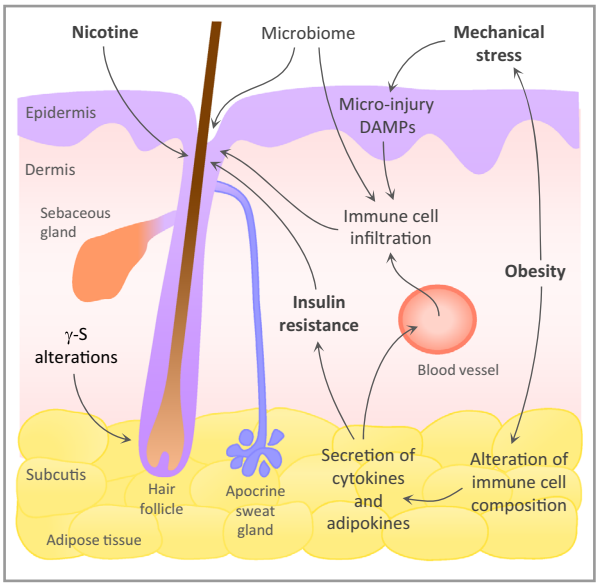

Figure 1 Predisposing factors in hidradenitis suppurativa (HS). The mechanisms of HS lesion formation centre around the pilosebaceous–apocrine units in the intertriginous skin areas. These areas differ from other skin areas by the higher temperature, higher moisture and reduced oxygen availability and, linked to these factors, a specific, anaerobe-enriched microbiome. Moreover, they show increased mechanical stress. The mechanical stress may induce cutaneous microinjuries that provoke release of cellular damage-associated molecules (DAMPs) and entry of microbiome components into the skin, both favouring local inflammation. The aetiopathophysiology involves both genetics and factors associated with patients' lifestyles. Although one-third of patients report a positive family history for HS, the responsible genetic features are unknown in most cases. A minority of patients with positive family history for HS show alterations in γ-secretase (γ-S) genes, which may contribute to follicular instability. The lifestyle factors involved in HS disease development are obesity and insulin resistance, as well as tobacco smoking. Central obesity (found in up to 60% of patients) is one of the factors defining the metabolic syndrome, which is found in a large proportion of patients with HS. Obesity enlarges the skinfolds in the body and, consequently, increases the mechanical stress, maceration and anaerobic conditions within those folds. Obesity also induces subclinical inflammation in the adipose tissue, with secretion of inflammatory cytokines (including interleukin-1β and tumour necrosis factor-α), which can reach the skin from the underlying subcutis or via the blood flow. Insulin resistance may alter the growth of keratinocytes. Inducing endothelial activation and chemokine production, inflammatory cytokines provoke the infiltration of immune cells from the blood, further supporting the inflammatory process in the skin. Smoking (found in up to 90% of patients with HS) induces nicotine exposition, which may favour infundibular acanthosis and dysbiosis, two of the initial events observed in HS pathogenesis. [Colour figure can be viewed at wileyonlinelibrary.com]

cells.[28] Beside obesity, insulin resistance/hyperglycaemia/type 2 diabetes mellitus might be an independent factor for HS.[29] The altered proliferation and differentiation of insulin-resistant keratinocytes may be one of the mechanisms underlying this association (Figure 1).[30] In turn, skin disease may favour obesity and metabolic syndrome, for example by induction of adipokines, insulin resistance and dyslipidaemia.[28]

Smoking is very common among patients with HS. Reports show up to 90% of patients currently or formerly smoking.[31] In line with that, the adjusted odds of developing HS among people who smoke compared with those who do not was 1·9.[32] Nicotine may induce epidermal hyperplasia and dysbiosis.[33–35] In monocytic cells, especially when exposed to bacterial components, nicotine may increase intracellular cAMP levels and strengthen the production of IL-10,[36–38] a cytokines that plays a role in HS (see below).

Apart from these factors, contribution of sex hormones is suspected.[39] This is based on the frequently observed onset of HS after puberty and the decreased disease severity during pregnancy.[39,40] In female patients, efficacy of antiandrogen therapy was suggested.[41]

Special features of skin areas predisposed to hidradenitis suppurativa

The specific nature of skin areas predisposed to HS alterations may give hints to factors that favour disease development. These areas (i.e. skinfolds in mostly axillary, inguinal, genital, gluteal and perianal body areas) contain a high density of pilosebaceous–apocrine units. They further differ from other areas by the higher temperature and moisture, reduced oxygen availability and, linked to that, the microbiome composition. In the skinfolds of healthy individuals, predominant taxa are Gram-positive aerobic and facultative anaerobic bacteria such as coagulase-negative *Staphylococcus* ssp. and *Corynebacterium* ssp., while strict anaerobes such as *Propionibacterineae* are detected with a low abundance (Figure 2).[42–44] Gram-negative anaerobic rods such as *Prevotella*, which are typical for mucosal sites, were also detected in very low numbers.[42,45] Interestingly, compared with matched areas in healthy individuals, the microbiome of clinically unaffected, HS-typical areas of patients with HS showed an increase in the relative abundance of *Prevotella* and other anaerobes and a decreased abundance of skin-surface-typical species like *Staphylococcus epidermidis*.[45] Pathogenetically, these resident anaerobic bacteria may support initial hair follicle inflammation in HS.

Being intertriginous, body areas predisposed for HS are also subject to skin friction, especially in obese patients. Mechanical stress induces skin microinjuries with release of cellular damage-associated molecules (also called DAMPs or alarmins) and cutaneous entry of microbiome components. DAMPs include nucleic acids, LL37, heat shock proteins, S100A15 and HMGB1,[46] some of which have been associated with HS lesions.[47,48] DAMPs and bacterial components stimulate local macrophages, dendritic cells and keratinocytes via their various PRRs[49–51] to produce inflammatory cytokines. Bacterial components are also recognized by and activate the complement pathway.[52] In fact, the constitutive subclinical inflammation in intertriginous areas is supported by recently suggested increased numbers of dendritic cells and Th cells with constitutive IL-17 expression at these sites.[53]

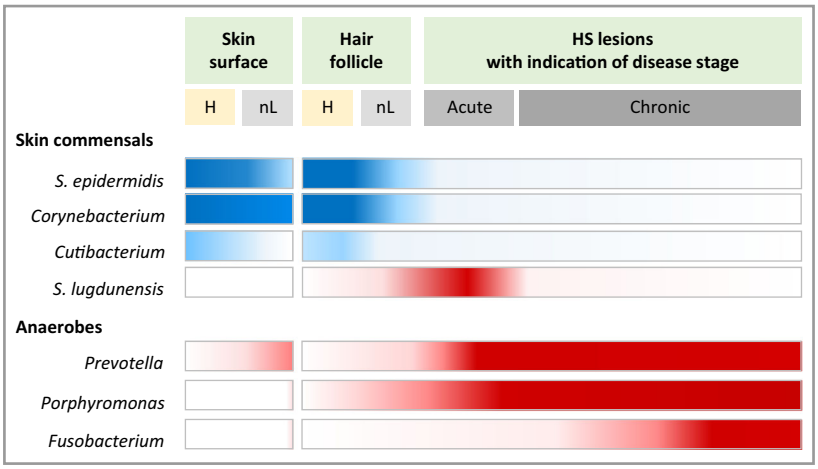

Figure 2 Bacterial skin dysbiosis in hidradenitis suppurativa (HS). Bacterial skin dysbiotic features of HS are presented, from the preclinical state to severe lesions, based on 16S rRNA gene amplicon sequencing data. Only representative taxa are shown. *Staphylococcus epidermidis* and *Corynebacterium* spp. are the main bacterial taxa of the normal skinfold microbiome. At the preclinical stage, the skin-surface microbiome of HS skinfolds is characterized by a decreased abundance of the skin commensals *Staphylococcus epidermidis* and *Cutibacterium* and by a moderate increase of *Prevotella*, a Gram-negative anaerobic rod. These dysbiotic features are more pronounced in HS lesions. Early modifications of the hair follicle microbiome are observed in HS with abnormal colonization with the Gram-negative anaerobic rod *Porphyromonas*. *Prevotella* and *Porphyromonas* are associated with chronic HS lesions. Some pathogens are associated with a specific form of HS: *Staphylococcus lugdunensis*, associated with acute mild HS nodules, and *Fusobacterium*, associated with chronic severe HS. The association level of the indicated bacterial taxa with the disease state is represented by blue–white (nonpathogenic bacteria) and red–white (pathogenic bacteria) gradients. H, skinfolds of healthy donors; nL, nonlesional HS skin. [Colour figure can be viewed at wileyonlinelibrary.com]

It should be noted that HS lesions can also develop in intertriginous areas that do not bear apocrine glands, such as submammary folds.[54,55] Thus, apocrine glands do not appear to be necessary for the development of HS lesions. Inflammation of these glands was demonstrated to be a secondary phenomenon.[56–58]

Pathogenetic processes

HS disease starts around the hair follicle.[59] The first histologically detectable events include infundibular acanthosis, hyperkeratosis and perifollicular immune cell infiltration (Figure 3).[56,57,60,61] Whether the immune cell infiltration or the infundibular alteration is the primary event that induces the other one has not been finally determined. Specific predisposing factors (Figure 1) directly induce immune cell infiltration (obesity), while others provoke infundibular acanthosis (nicotine).

The infundibular alterations lead to follicular occlusion and consequent stasis with dilatation of the hair follicle (Figure 3).[1] This may lead to multiplication of anaerobic bacteria within the occluded hair follicles, as suggested by 16S rRNA gene amplicon sequencing.[62] Bacterial components and DAMPs released from damaged follicular cells may further stimulate inflammatory responses in local cells, especially macrophages. The PRRs activated by these stimuli include Toll-like receptor 2 and the inflammasome component NLRP3, both of which are upregulated in HS skin[63–65] and mediate the release of cytokines such as IL-1β and tumour necrosis factor (TNF)-α. These pleiotropic mediators have two major functions that support immune cell infiltration into the tissue: the activation of endothelia and the induction of chemokine production by local tissue cells (Figure 3). The influx of neutrophilic granulocytes might be further promoted by leukotriene B4, a lipid mediator that is produced by macrophages via hyperactivation of the 5-lipoxygenase pathway in HS.[66]

Individual proinflammatory cytokines are strong inducers of extracellular matrix-degrading enzymes, the matrix metalloproteinases (MMPs).[64] At this stage, these enzymes may be involved in the thinning of the basement membrane surrounding the hair follicle unit, as detected in perilesional HS skin. This thinning may increase the fragility of the inflamed and dilated hair follicle.[67] In γ-S-associated familial HS, the potential decrease of notch-mediated support of the hair follicle epithelium could also reduce the stability of the hair follicle unit. The consequence of these processes probably favours the rupture of the hair follicle (Figure 3). Hair follicle stem cells in HS lesions show an increased proliferation rate. This is associated with elevated numbers of micronuclei and presence of cytoplasmic single-stranded DNA in proliferating cells.[68] Activating PRRs, cytoplasmic DNA might also strengthen local inflammation.

The release of the content of ruptured hair follicles (including bacteria, DAMPs, keratin fibres and sebum components) into the surrounding tissue massively boosts inflammation. Inflammation eventually leads to clinically visible dermal nodules and abscesses. The formation of pus-draining epithelialized sinus tracts and fistulas may be supported by the continued formation of pus, known to occur in the massive presence of neutrophilic granulocytes and bacteria, the seeding

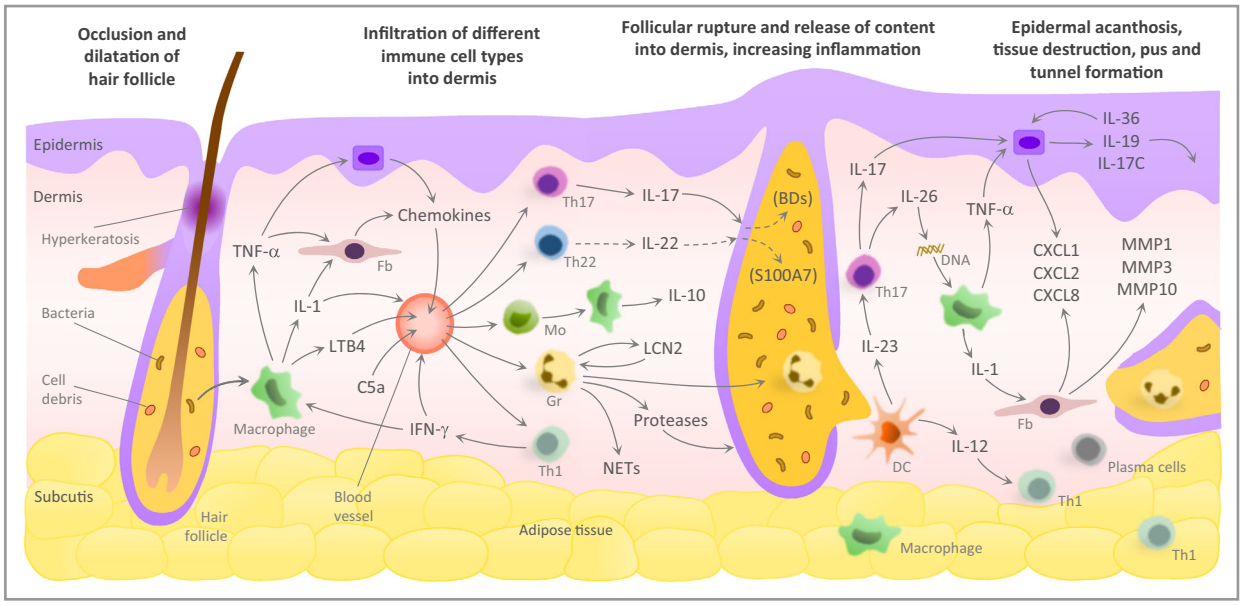

Figure 3 Pathogenetic events in hidradenitis suppurativa (HS). Disease-predisposing factors (Figure 1) induce perifollicular immune activation as well as occlusion, sebum stasis, and dilatation of the hair follicle unit. This leads to growth of bacteria within the occluded hair follicles and release of damage-associated molecules, which stimulate local immune cells, especially macrophages, to produce inflammatory cytokines like tumour necrosis factor (TNF)-α and interleukin (IL)-1β. Via their epithelium-activating and chemokine-inducing properties, these cytokines provoke the infiltration of various immune cell populations. These include neutrophilic granulocytes, monocytes (which in the skin can differentiate into macrophages or dendritic cells), B/plasma cells, and different functional subgroups of effector/memory T cells (which had been generated in the skin-area-associated draining lymph nodes). While T helper (Th)1 cells and Th17 cells and their main mediators interferon (IFN)-γ (Th1), IL-17A/F and IL-26 (Th17) become abundant in HS skin, Th22 cells and IL-22 are not. Due to the limited upregulation of IL-22, epidermal production of antimicrobial proteins [including β-defensins (BDs) and S100A7] is too low to confine cutaneous bacterial growth. Neutrophilic granulocytes, whose infiltration is supported by chemokines (e.g. CXCL1, 2 and 8, which are highly produced by dermal fibroblasts), leukotriene B4 (LTB4), the complement component C5a and lipocalin (LCN)2, are important phagocytes and producers of proinflammatory cytokines. These cells also form neutrophil extracellular traps (NETs), which can inhibit bacterial growth but also favour autoimmune features. Infiltrated B/plasma cells produce antibodies and may contribute to the activation of the complement system. Secreted proteolytic enzymes may further increase the fragility of the basement membrane surrounding the hair follicle unit. The amount of bacteria within HS skin lesions increases, with progressively reduced frequency of prototypical skin commensals and high enrichment of strictly anaerobic Gram-negative species. Bacterial growth further boosts inflammation. The inflammatory process and hair follicle fragility lead to rupture of the hair follicle unit with release of its immune-stimulatory content into the surrounding tissue. Continuous inflammation with pus formation, epithelialization within the disintegrated tissue, and abundance of extracellular matrix-degrading enzymes (matrix metalloproteinases, MMPs) finally lead to the formation of pus-draining epithelialized tunnels and destruction of skin architecture. Self-amplifying inflammatory pathways that involve many further cytokines (e.g. IL-17C, IL-19, IL-36 and LCN2) and persistent anaerobic bacteria support the chronification and recurrent nature of lesions. DC, dendritic cell; Fb, fibroblast; Gr, neutrophilic granulocyte; Mo, monocyte. [Colour figure can be viewed at wileyonlinelibrary.com]

of follicular stem cells into the disintegrated tissue,[67] the abundance of MMPs,[64] and the loosening of cell–cell adhesive junctions in the epidermis[69] (Figure 3). Chronification of inflammation leads to destruction of skin architecture, recurring development of abscesses, wounding, and subsequent fibrotic scarring.[1] Macrophage-dependent chronic WNT activity may play a role in fibrotic scarring.[70] HS lesions and adjacent areas also contain areas of interfollicular inflammation with acanthosis, as known from psoriatic skin.[56–58,71]

Established HS lesions contain massive immune cell infiltrates. Apart from neutrophilic granulocytes, macrophages and dendritic cells are the most abundant cells. Furthermore, T cells, mast cells, natural killer cells and B/plasma cells are found.[57,65,71,72] Neutrophilic granulocytes are important phagocytes of bacteria and producers of proinflammatory cytokines, and they have the ability to release antimicrobial and cytotoxic molecules by degranulation. Furthermore, these cells form neutrophil extracellular traps (NETs), which have been detected in HS lesions.[73] These web-like structures are composed of a scaffold of decondensed chromatin loaded with cytosolic and granule proteins.[74] In HS, lesional NET formation has been suggested to be linked to the presence of autoantibodies.[73]

Surprisingly, the extent of T-cell infiltration in HS lesions is comparable with that found in psoriasis,[21] a well characterized T-cell-mediated chronic inflammatory skin condition.[75] T cells, after being primed in the regional lymph nodes, circulate through blood and lymph nodes (central memory T cells) or exert their effector functions in the tissue (effector T cells, effector/memory T cells).[75] B/plasma cells may be part of

lymphoid structures formed in chronically inflamed peripheral tissues.[76] B cells serve as antigen-presenting cells and as producers of antibodies and anti-inflammatory and proinflammatory cytokines. Apart from antigen neutralization, antibodies may contribute to the complement activation seen in HS.[52]

In the course of HS pathogenesis, bacteria become abundantly present within HS skin lesions, with their composition further changing compared with the microbiome of unaffected intertriginous skin (Figure 2). *Staphylococcus lugdunensis*, an opportunistic pathogenic coagulase-negative *Staphylococcus* species, was detected in 25% of nodules as the sole or predominant pathogen, but not in chronic suppurative lesions.[77] Interestingly, *Staphylococcus aureus*, a well-known cause of folliculitis, furuncles and acute skin abscesses, is not associated with HS.[43,77] Chronic lesions show clearly reduced abundance of prototypical skin commensals and high enrichment of strictly anaerobic Gram-negative bacteria such as *Prevotella* and *Porphyromonas* ssp., along with *Streptococcus anginosus* and *Actinomyces* spp., which often cause opportunistic infections (Figure 2).[43,78] Furthermore, *Fusobacterium nucleatum*, a Gram-negative anaerobic rod with invasive properties, is associated with the most severe form of HS.[43,77,79]

Together, HS lesions show abundance of opportunistic pathogens but not highly pathogenic bacteria and commensals. Accordingly, optimized antibiotic treatment demonstrated therapeutic efficacy especially in patients with HS with mild disease, but required much longer treatment times than in classical soft tissue and skin infections.[80–82] Bacterial colonization appears important due to immunostimulatory effects unrelated to a proper infection.[83] Some studies showed increased biofilm formation, especially within inflamed hair follicles and tunnels.[84] The epidermal antimicrobial defence mechanisms in HS lesions appear too weak to counteract local bacterial growth effectively (see below).

Role of specific cytokines in hidradenitis suppurativa

A broad range of immune mediators are highly expressed in established HS lesions compared with healthy control skin.[21,64] Interestingly, most of them are also upregulated in psoriasis,[21,64] which indicates an overlap of certain pathogenetic pathways in both diseases. This supports the clinical investigation of approved antipsoriatic drugs that target respective immune mediators for use in HS. On the other hand, there is a range of cytokines whose levels in HS exceed or are clearly below the levels in psoriasis[21,64] that could point to HS-specific alterations.

Among the mediators known to be mainly produced by macrophages, HS lesional skin shows high levels of the proinflammatory cytokines TNF-α and IL-1β.[21,63,64,85,86] TNF-α mRNA reaches levels similar to those in the inflamed skin of patients with psoriasis,[21,64] a disease that strongly responds to anti-TNF-α therapy.[87] IL-1β upregulation in HS skin greatly exceeds that in psoriatic skin[64] and is not associated with raised levels of the natural IL-1 inhibitor, IL-1 receptor antagonist.[64] The expression of IL-1α, which shares with IL-1β the cellular receptor complex (Figure 4),[88] is also increased in HS lesions compared with healthy donor skin, but this increase is much less pronounced.[64] For secretion of IL-1 protein, the inflammasome system, which represents an integrated PRR/effector system assembling after activation by danger-associated and bacterial molecules, is responsible. HS lesions show increased expression of NLRP3 and P2X7 (the ATP receptor and an inflammasome activator) and increased caspase 1 activity.[63,64,89] *Ex vivo* analysis of IL-1β protein secretion by different cell populations isolated from lesional HS skin demonstrated macrophages as a major IL-1β source,[64] although lesional keratinocytes were also able to produce this cytokine.[86]

TNF-α acts on most cells in the body, using two alternative transmembrane receptors (Figure 4) with different biological responses. In the skin, TNF-α induces a wide range of immune-cell-attracting chemokines and contributes to endothelial activation, favouring immune cell infiltration.[90] This function is crucial to each immunological response; it is therefore not surprising that the TNF-α-targeting antibody adalimumab is approved not only for HS[91] but also for psoriasis and psoriasis arthritis, spondyloarthritis and spondyloarthropathy, and Crohn disease.[92–94]

IL-1β also influences every cell type, although, among skin cells, dermal fibroblasts showed the highest IL-1 receptor levels and the strongest IL-1 responses.[6] IL-1β induces the production of MMPs (MMP1, MMP3, MMP10) and various chemokines, with those attracting neutrophilic granulocytes (CXCL1, CXCL6, CXCL8) being most prominent. Moreover, IL-1β induces specific cytokines in its target cells, including IL-6, IL-32 and IL-36β.[64] While the effects of IL-1β on fibroblasts are not clearly shared by other proinflammatory cytokines, in keratinocytes they are often amplified by TNF-α and IL-17. IL-1β target molecules are highly abundant in HS skin.[21,47,64,95,96] The relationship between IL-1β and its target molecules was clearly supported by the reduction of the expression of these target molecules in explanted skin from HS lesions, when treated with an IL-1 receptor antagonist.[64] MMPs may be involved in the early rupture of the hair follicle units and the later loosening of epidermal cell–cell junctions during tunnel formation. Neutrophils attracted by the IL-1-induced chemokines (and maybe by leukotriene B4 and the complement component C5a) contribute to inflammatory cytokine production and pus formation in HS.

Among the cytokines produced by neutrophils in HS (especially after TNF-α stimulation) is lipocalin 2.[97] Apart from its role in inflammatory pain and metabolic control, lipocalin 2 supports further neutrophil tissue infiltration.[98,99] A recent study suggested production of the cathelicidin-derived peptide LL37 by these cells, which the authors claimed to support T-cell proliferation in HS lesions.[47] While little is known about the role of IL-32, IL-6 seems to influence a large range of cells via two alternative signalling ways, involving a membrane-bound and a soluble receptor.[100] In HS lesions, it may, similarly to IL-1β, favour the function of Th17, while impairing

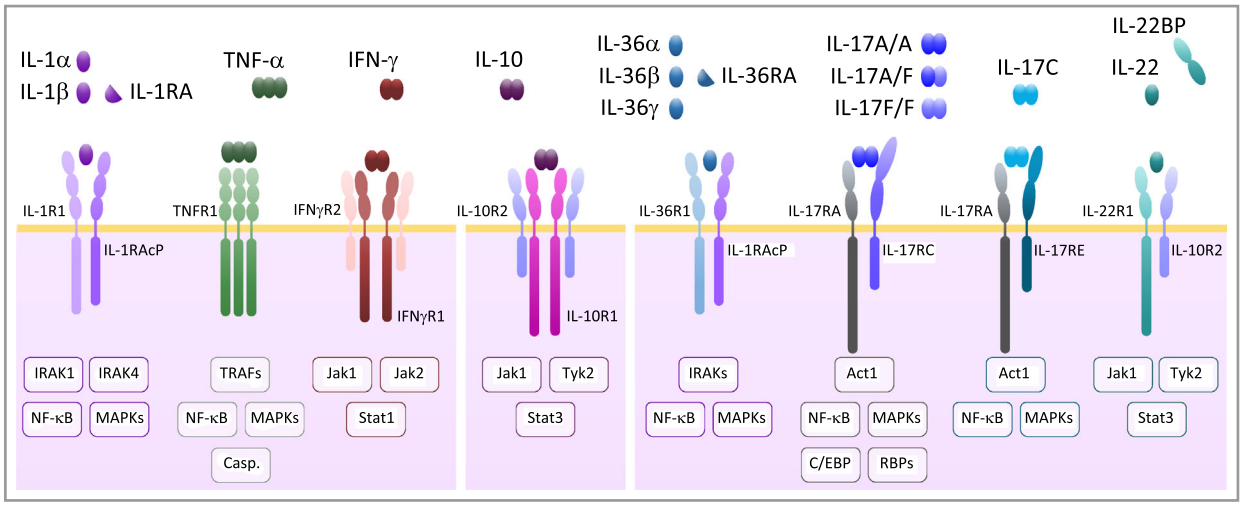

Figure 4 Cytokines involved in hidradenitis suppurativa (HS) pathogenesis and their receptors. The structures and major downstream signalling factors of the receptor complexes used by cytokines involved in HS pathogenesis are depicted. The expression pattern of the receptor complexes determines the target cells of the cytokines. While some cytokines largely act on both immune and tissue cells [e.g. interleukin (IL)-1β, tumour necrosis factor (TNF)-α and interferon (IFN)-γ], some mainly target immune cells (IL-10) or tissue cells (e.g. IL-22). Therapeutic inhibition of the action of cytokines is possible via neutralization of the cytokines themselves, blocking their specific receptors or interfering with the activation of signalling elements downstream to the receptors. BP, binding protein; Casp., caspases involved in apoptosis; C/EBP, CCAAT-enhancer-binding protein; IRAK, IL-1 receptor-associated kinase; Jak, Janus kinase; MAPK, mitogen-activated protein kinase; NF, nuclear factor; R, receptor; RA, receptor antagonist; RAcP, receptor accessory protein; RBP, RNA-binding protein; Stat, signal transducer and activator of transcription; TRAF, TNF receptor-associated factor; Tyk, tyrosine kinase. [Colour figure can be viewed at wileyonlinelibrary.com]

the function of regulatory T cells.[101–104] Moreover, IL-6 supports the function of B cells.[100]

Interestingly, in addition to the proinflammatory cytokines, the anti-inflammatory cytokine IL-10 is prominently expressed in HS lesional skin.[21,63,86,105] Macrophages may be the main source of IL-10 in HS. In these cells, IL-10 can be induced by bacterial components and cytokines like TNF-α. Intracellular cAMP levels, induced by nicotine, may further support cutaneous IL-10 production in patients with HS who smoke.[36,37] IL-10 exclusively acts on immune cells via a dimeric receptor complex (Figure 4).[106–108] In myelomonocytic cells, IL-10 strengthens the phagocytosis of bacteria and the clearing away of the apoptotic cells.[109] IL-10 also limits the T-cell stimulation capacity of and proinflammatory cytokine production by monocytes and macrophages.[110–112] Moreover, IL-10 can directly inhibit cytokine production in T cells (see below).[21,113,114]

Among T-cell-typical mediators, the Th17 cell cytokines IL-17A and IL-17F, as well as the Th1 cell cytokine IFN-γ, are highly expressed in HS lesions, with levels comparable with those in psoriasis.[21,64] In contrast, IL-22 shows only limited upregulation.[21] In line with this, HS lesions show an abundance of Th cells able to secrete IL-17 and IFN-γ, but not IL-22.[86] The production of IL-17 and IFN-γ by Th cells (typically Th17 and Th1 cells, respectively) is known to be supported by IL-23, IL-1β and IL-6 (IL-17), as well as by IL-12 (IFN-γ),[75] which are all upregulated in HS lesions.[21] IL-12 and IL-23 were found to be abundantly expressed by macrophages infiltrating the papillary and reticular dermis of lesional skin.[115] Moreover, IL-17 and IFN-γ production is supported by mammalian target of rapamycin (mTOR) complex signalling,[116,117] whose relevance might be deduced from the reported increased mTOR expression in HS lesions.[118]

IL-17A and IL-17F form homo- and heterodimers and share a cellular receptor complex (Figure 4).[119] Their main target cells are epithelial cells, but effects have also been detected on fibroblasts and endothelial cells, for example. IL-17A and IL-17F induce the production of selected chemokines (such as CCL20, attracting Th cell subpopulations and dendritic cells, as well as those specific for neutrophilic granulocytes, such as CXCL1 and CXCL8), cytokines (such as the IL-17 action-enhancing cytokine IL-19) and antimicrobial proteins (AMPs; such as β-defensin-2 and S100A7).[120–124] AMPs are key players in the epidermal immune defence against extracellular bacterial and fungal pathogens. While on their own, IL-17A and IL-17F cause only moderate cell responses, their function lies primarily in the synergistic action with other tissue-active cytokines such as TNF-α, IL-22 and IFN-γ.[123–129] The consequent involvement of IL-17A/F in various cutaneous inflammatory pathways and the high efficacy of approved IL-23 and IL-17 inhibitors in psoriasis led to initiation of clinical studies testing those biologics in HS.[1]

Another Th17 cell cytokine upregulated in HS lesions is IL-26.[21,130] Its biology differs from that of IL-17A/F. While its receptor-dependent cytokine properties are debated, IL-26 directly kills bacteria, an effect that is impaired in HS.[130] Furthermore, IL-26 acts as a carrier of DNA released from damaged cells to intracellular DNA-binding PRRs. The resulting

PRR activation, for example in macrophages, induces an inflammatory response.[131]

IFN-γ is a pleiotropic Th/Tc1-cell cytokine that affects both tissue and immune cells via its tetrameric cellular receptor complex (Figure 4).[132] IFN-γ induces chemokines such as CXCR10[133] that attract Th/Tc1 and natural killer cells and that are also upregulated in the skin of patients with HS.[85,134] Moreover, IFN-γ supports the activation of dermal endothelia.[132] It also strengthens proinflammatory cytokine production by macrophages and regulates B-cell functions. On both tissue and antigen-presenting immune cells, it upregulates the surface expression of the major histocompatibility complex and costimulatory molecules, which may be important for local T-cell activation in HS.[132]

The limited upregulation of IL-22 in HS lesions is due to both the limited increase in the frequency of IL-22-producing Th cells, as reported by Hotz *et al.* (see above),[86] and the inhibited production of this cytokine by Th cells. Regarding the latter, IL-10 might be involved, as deduced from the inhibitory effect of IL-10 on IL-22 production *in vitro* and the negative correlation between lesional levels of IL-22 and IL-10 in HS.[21] Not only the production but also the impact of IL-22 may be limited in HS. This was concluded from the increased expression of IL-22-binding protein,[21] the natural soluble receptor that inhibits the cutaneous action of IL-22.[135,136] In the skin, IL-22 acts exclusively on keratinocytes.[137,138] Like IL-17, IL-22 is an inducer of epidermal AMPs.[137] It does so both directly and via the induction of IL-20, its downstream mediator, which shares with IL-22 a receptor complex subunit (IL-22R1) (Figure 4).[21,129,137]

Regarding AMP induction, IL-22 acts with IL-17 in a synergistic manner, and only the strong presence of both cytokines results in strong AMP upregulation, which is essential for the protection of disturbed skin.[21,124,137] Consequently, the relative IL-22 deficiency in HS lesions leads to minimal AMP upregulation.[21,96] This may explain the abnormal bacterial colonization of HS lesions and the elevated frequency of skin infections in respective patients.[139] IL-22 also acts as an inhibitor of cellular differentiation and a protector against cellular damage.[138,140–142] Therefore, the limited IL-22 production in HS may also be related to the destructive nature of the HS inflammation. Finally, IL-22 is a regulator of metabolism.[143]

Among the mediators known to be produced by skin tissue cells, HS lesions show increased expression of IL-36α, IL-36β and IL-36γ, which were mainly localized to keratinocytes.[47,64,144,145] The IL-36 receptor (Figure 4) is expressed by tissue cells including keratinocytes, as well as monocytic immune cells and T cells.[146] IL-36 cytokines are known for their induction of neutrophil-attracting chemokines, specific cytokines and AMPs.[147,148]

Another tissue-cell cytokine highly expressed in HS lesional skin is IL-17C.[149] IL-17C is part of the IL-17 cytokine family.[150] It is induced by proinflammatory cytokines including IL-1β and TNF-α, and to a lower extent by IL-17A, as well as by bacterial components.[151] The IL-17C receptor complex (Figure 4)[151–153] is mainly expressed by epithelial cells including keratinocytes,[151] but is also expressed by Th17 cells.[153] Interestingly, the (autocrine) responses induced by IL-17C in keratinocytes are very similar to those induced by IL-17A/F.[151,154]

Some of the inflammatory cytokines and their target molecules produced in HS lesions are also detectable in the circulation.[47,64,95,97,155–159] They may act systemically and support comorbidities in these patients.[1] Furthermore, they may be useful as indicators of the activation of specific immunological pathways in the skin. They could also enable the identification of patients at risk for specific comorbidities. A range of efforts have been made to identify such biomarkers also beyond cytokines.[52,160,161]

Conclusion

HS is a complex, immunologically mediated disease that involves different components simultaneously: an inflammasome-driven innate component with dominance of neutrophilic granulocytes, a significant anti-inflammatory component, and strong activation of the Th1 and the Th17 pathways, but not the Th22 pathway. Anaerobic bacteria and cell-damage-associated molecules play an inflammation-triggering role. Activated pathways induce inflammatory vicious circles resulting in pain, purulence, tissue destruction and scarring. Several clinical studies are currently being carried out that aim to prevent the action of cytokines such as IL-17, IL-23p19 and IL-1,[1] the roles of which are described above. Prevention of cytokine action is possible by neutralization of the cytokines themselves, blocking their specific receptors or interfering with their signal transduction (Figure 4). Not only the pathogenetic complexity but also the destructive nature of HS represents a challenge for the development of therapeutic approaches for this disease. In fact, once the skin architecture is damaged, it cannot be repaired with medications. Therefore, great efforts are needed to reduce the current intolerable delay in the diagnosis of HS[162] as a prerequisite for an early start of anti-inflammatory treatment. An early treatment start may also prevent or counteract the systemic comorbidities and reduced life expectancy of patients with HS.

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