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What causes hidradenitis suppurativa? — 15 years after

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Abstract

The 14 authors of the first review article on hidradenitis suppurativa (HS) pathogenesis published 2008 in EXPERIMENTAL DERMATOLOGY cumulating from the 1st International Hidradenitis Suppurativa Research Symposium held March 30–April 2, 2006 in Dessau, Germany with 33 participants were prophetic when they wrote “Hopefully, this heralds a welcome new tradition: to get to the molecular heart of HS pathogenesis, which can only be achieved by a renaissance of solid basic HS research, as the key to developing more effective HS therapy.” (Kurzen et al. What causes hidradenitis suppurativa? Exp Dermatol 2008;17:455). Fifteen years later, there is no doubt that the desired renaissance of solid basic HS research is progressing with rapid steps and that HS has developed deep roots among inflammatory diseases in Dermatology and beyond, recognized as “the only inflammatory skin disease than can be healed”. This anniversary article of 43 research-performing authors from all around the globe in the official journal of the European Hidradenitis Suppurativa Foundation e.V. (EHSF e.V.) and the Hidradenitis Suppurativa Foundation, Inc (HSF USA) summarizes the evidence of the intense HS clinical and experimental research during the last 15 years in all aspects of the disease and provides information of the developments to come in the near future.

KEYWORDS
acne inversa, hair follicle, hidradenitis suppurativa, inflammatory skin diseases, pathogenesis
remains to be done, but convincing evidence that proinflammatory cytokines play a central role, that opening the possibility of targeted treatment, has led to clinical trials and regulatory approval of adalimumab for treatment of HS. In turn, this has spurred a flurry of new trials with different drugs. Trials need endpoints, and with fortuitous premonition, a structured search for evidence-based outcome variables has been performed by the European Hidradenitis Suppurativa Foundation (EHSF) e.V. and is also on its way led by the HISTORIC group. Many other efforts are underway to understand HS and optimize the management of this hitherto secret scourge. Expect the future to bring much good for the many HS patients.

2 | INFECTION, AUTOIMMUNITY OR BOTH?

The role of bacterial infections per se as the primary cause of HS has attracted a lot of controversy evolving knowledge as to the underlying pathogenesis. A wide range of bacteria, including Staphylococcus aureus, coagulase-negative staphylococci, Corynebacterium species and anaerobic agents, such as Porphyromonas, Prevotella and Fusobacterium, have been isolated from deep HS lesions. Indeed, bacteria may act in HS as pathogen-associated molecular triggers of inflammation by creating patterns linking their receptors, including the transmembrane toll-like receptors and intracellular Nucleotide binding Oligomerization Domain (NOD)-like receptors. A down-regulation of the alarmins/antimicrobial peptides S100A7 and S100A9 as well as an increased expression of antimicrobial cathelicidine LL-37 has been detected in HS lesional skin, suggesting an innate immunity dysfunction leading to an altered host-microbiome crosstalk.

Reports on the coexistence of HS with autoimmune diseases, such as systemic lupus erythematosus, and autoinflammatory conditions, such as Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO) syndrome, support the role of autoimmunity/autoinflammation in HS pathogenesis. Interleukin (IL)-1β is a highly prominent cytokine in lesional skin of both classic HS and Pyoderma gangrenosum, Acne, Suppurative Hidradenitis (PASH) syndrome, the main syndromic form of HS. This cytokine plays a crucial role in autoinflammation, suggesting that there is an important autoinflammatory component in the HS pathogenesis. This view is further supported by genetic mutations which are shared between HS and classic autoinflammatory diseases. The latter encompass a huge spectrum of conditions characterized by episodes of neutrophil-driven, sterile inflammation in the affected organs, including the skin.

As a consequence of these mutations, the inflammasome, which is a protein complex in neutrophils and macrophages, activates the autoinflammatory process through an uncontrolled release of several proinflammatory cytokines such as IL-1, IL-17, IL-23 and Tumor Necrosis Factor (TNF)-α, all overexpressed in HS lesional skin. With several new gene mutations coming into play, such as those involved in the γ-secretase complex and in the keratinization pathway, on the background of alterations in the skin microbiome, HS can be regarded as a multifactorial, polygenic, autoinflammatory disease (Figure 1).

3 | MUTATIONS AND HS: WHAT IS VALID?

Mutations of γ-secretase complex (GSC) genes PSENEN, PSEN1 and NCSTN were first described in familial HS 10 years ago. Mutations have since been reported in at least 41 patients or families worldwide, including 16 Chinese, 4 Japanese, 4 Jewish Ashkenazi, 3 French, 2 British, 2 Indian, 1 African American, 1 American (Caucasian), 1 German and 1 Dutch kindreds, 4 sporadic cases (2 British, 1 Afro-Caribbean and 1 American) and 2 patients with unknown familial history. The reported 41 mutations of GSC genes include 28 in NCSTN, 12 in PSENEN and one in PSEN1, of which 12 are frameshifts, 11 result in nonsense mutations, 9 in missense mutations and 9 are splice site mutations. GSC is an intramembrane protease complex able to cleave more than 90 transmembrane proteins. Mutations in GSC could affect activation of presenilin, prevent substrate binding and hinder intramembrane cleavage of select proteins. Most of the PSENEN gene mutations are associated with the “clinical subphenotype” of Dowling-Degos disease. In HS patients with NCSTN mutations, remarkable findings are the male predominance (1.7:1 vs 1:3 in regular HS) and the characteristic phenotype. Overall, GSC gene mutations occur only in around 6% of non-familial HS. Several other mutations have been associated with (syndromic) HS including MEFV, POFT1, PSTPIP1 and FGFR2. An intriguing question is what the functional consequences are of all these mutations and their causality. The GSC mutations were initially linked to decreased Notch signalling. Loss-of-function mutations would result in abnormal follicular differentiation, keratinization, occlusion and cyst formation. However, no significant differential expression of Notch 1-4 was identified in HS lesional skin as well as other inflammatory dermatoses including psoriasis, alopecia areata and atopic dermatitis. GSC-related proteases, ADAM10 and ADAM17, seem more likely candidates. ADAM17 is associated with inflammatory bowel disease and involved in epidermal, ductal and hair follicle formation, and production of matrix metalloproteinases. Furthermore, Nicastrin mutations interact with ADAM17 activity. Functional studies comprising GSC substrates other than Notch, including epigenetic, environmental and metabolic factors, should be considered. Other genetic approaches in regular non-familial HS, such as GWAS or exome-sequencing, are highly needed to discover new inflammatory pathways that may lead to novel therapeutic targets for this debilitating condition.

One large scale study using one Greek cohort and another German cohort identified that carriers of more than six copy numbers of the β-defensin (hBD2) gene cluster of chromosome band 8p.23.1 had greater risk for the acquisition of HS (odds ratio 6.72). Carriage of more than six copy numbers was associated with less severe disease phenotype regarding the degree of purulence and
the number of affected body areas. These patients were prone to high production of hBD2 from whole blood upon stimulation with Staphylococcus aureus.\textsuperscript{39}

4 | SKIN TRANSCRIPTOME IN HS

HS personalized medicine relies on understanding the molecular taxonomy and heterogeneity among HS patients. With the fast-evolving HS therapeutic landscape, defining the right drug for the right patient at the right time is critical. Currently, only adalimumab, a TNF-\(\alpha\) inhibitor, is approved for treatment of HS moderate-severe disease, but interest exists for targeting additional immune factors.

Great strides have been achieved through HS skin transcriptomic studies initiating an in-depth investigation of the molecular events of HS disease.\textsuperscript{4,40-43} The analysis of the HS transcriptome has provided unforeseen signatures of inflammatory, epithelial, hair follicle and sweat gland signalling molecules: Early innate immune responses including the upregulation of the alarmins S100A7, S100A7A and S100A8/A9; downregulation of the eccrine sweat gland-specific antimicrobial peptide dermcidin and induction of proinflammatory cytokines IL-1, IL-17, TNF-\(\alpha\) and interferons (Figure 2). Aberrant adaptive immunity with marked increase in T and B cells and plasma cell signatures in HS could point to autoimmune causes or simply reflect the result of chronic inflammation in late-stage HS. Importantly, most of the previous transcriptomic studies were small and focused on moderate-severe HS limiting identification of potential HS disease drivers through early innate immune disease-associated molecules. Large cohort transcriptomic studies including early and minimal HS disease in addition to moderate and severe cases and skin sample collection from lesional and anatomical site-matched non-lesional skin are required to identify reliable and potentially predictive biomarkers (Figure 2). Beyond microarray and whole-genome RNA sequencing, novel single cell sequencing and spatial resolution approaches are pivotal to the understanding of HS heterogeneity and immunobiology aiming at defining specific endotypes. This will ultimately herald the development of personalized treatment approaches (Figure 2). Such approaches are currently pursued through collaborative initiatives in other diseases and have shown success.\textsuperscript{44-46}
Racial Background and HS

The role of race in HS pathogenesis is poorly understood. Observed differences in HS prevalence across epidemiologic studies are probably better explained by disparate study methodologies than by true geographic and demographic differences. In the United States, those of African American and biracial ancestry are disproportionately affected by HS, and this difference is even greater among adolescents. In Brazil, Amerindians are less likely to develop HS compared to other racial groups. Several studies have highlighted racial differences in the clinical characteristics of HS. In Western Europe and America, HS is more common in women compared to men. However, studies from eastern nations including Singapore, South Korea, Malaysia and Japan, Turkey, Malta, and Tunisia have observed higher prevalence in men. This male preponderance may be partially confounded by the relatively higher frequency of smoking among Asian men compared to women. Glutetheal distribution has been observed more frequently in Asian than in European and American HS cohorts, possibly related to male predominance in the Asian cohorts. Data regarding HS severity by race conflict with one study suggesting that African American patients may have earlier disease onset and are more likely to present with advanced disease compared to Whites.

Genetic studies have identified several γ-secretase mutations linked to HS pathogenesis. Although these mutations were initially reported in Han Chinese families, the same mutations have subsequently been detected in HS patients worldwide. It is unknown...
whether the prevalence of these mutations differs by race; however, known γ-secretase mutations explain the minority of familial HS cases.

Much remains to be learned about the influence of race on the pathogenesis of HS. Unfortunately, the vast majority of HS studies have failed to report participants’ race or ethnicity. Adequate representation of diverse patients across all demographic groups including race and ethnicity is critical to enhancing our understanding of disease pathogenesis and ensuring that treatments can meet the needs of all subgroups affected by this debilitating disease.

6 | DO PHENOTYPES INDICATE GENOTYPES?

The clinical presentation of HS, regardless of severity, is undeniably heterogeneous. For instance, some patients form many cysts, lesions at ectopic locations, other form mainly perianal heavily inflamed deep tunnels or superficial plaques on the body, while others form mainly superficial lesions resulting in ice-pick like scarring. Because of this variety in presentation, different phenotypes are very likely to exist. Identifying these phenotypes could be of critical relevance since different phenotypes could have variable prognosis and require different treatment strategies. One example based on geography is that Asian HS patients are more likely to be male and have gluteal disease. Whether this relates to differences in genotype, for example mutations in gamma secretase, remains to be investigated.

In 2013, Canoui-Poitrine et al were the first to propose three phenotypes. However, it received little attention for a long period of time. Currently, the age of biologic HS treatment is fuelling HS research and phenotypes are more relevant than ever. More recently, Martorell et al as well as van der Zee et al proposed a set of phenotypes. However, there are still important obstacles to overcome. For instance, the Canoui-Poitrine types have only a modest inter-rater reliability and are therefore of limited use in clinical practice and research settings. The clinical importance of the Martorell phenotypes has yet to be tested and the van der Zee types have not been statistically tested.

For future use to guide treatment, phenotypes must be clinically distinctive and have a high inter- and intra-rater reliability. The importance of this was recently demonstrated when Frew et al attempted to retrospectively label phenotypes to previous genetic HS publications. A repeat of the process by another group resulted in a very different outcome.

At the moment, the problem shared by all these phenotypic classifications is that they are based on analysis of relatively few cases and most are retrospective. The data do not always include all of the phenotypic features and comorbidities. An agreed minimum HS phenotype dataset may be needed to ensure that different datasets can be combined to increase statistical power.

Over recent years, the HS community has grown and we support efforts to study phenotypes in a prospective, large, international collaborative fashion with simultaneous collection of DNA for phenotype-genotype comparison.

7 | SKIN MICROBIOTA AND HS

Although HS was considered for many years to be purely inflammatory, recent extensive microbiology studies demonstrated the constant presence of commensal opportunistic bacterial flora within lesions, isolated in 4-7 days by culture and confirmed by 16S-ribosomal RNA-gene-amplicon-sequencing. 16S-sequencing also demonstrated that microbiology correlates with Hurley’s stage. In half of Hurley stage I lesions, skin pathogens are isolated alone, either Staphylococcus lugdunensis (25%) or Cutibacterium spp (25%). In the other half of Hurley stage I lesions, in Hurley stages II and III lesions, the flora is polymicrobial, with predominance of strictly anaerobic species (Prevotella and Porphyromonas being the most abundant), but also includes aero-tolerant anaerobes: Actinomyces spp, Streptococcus anginosus group, and Corynebacterium spp, with lack of Staphylococcus epidermidis and Cutibacterium spp, usually present in control skin. Flora variety and richness increase with severity.

Dysbiosis was confirmed in uninvolved HS skin by 3 teams, explaining constant relapses in previous scars.

An immune deficiency towards commensal gut flora was reported in patients with Crohn’s disease carrying a NOD2 mutation, while some HS patients can present with both diseases.

All these data suggest a pathogenic role of the isolated flora, introducing a new concept of host-microbiome disease for HS. Instead of a purely autoimmune process with an unclear mechanism, HS could be considered as “auto-infectious,” due to a strictly cutaneous immune dysregulation. This deficiency would allow abnormal bacterial proliferation with toxin production and an inappropriate hyper-inflammatory host response, instead of bacterial elimination from the dermis. This model could open avenues for novel treatments and research for HS and associated diseases. Many questions remain concerning HS microbiology. Is early microbial shift contributing to follicular occlusion? Could loss of the “microbial shield” be partially restored with immunomodulation or microbiota transplantation, as explored in inflammatory bowel disease?

Future microbiology studies should aim at demonstrating an abnormal transcriptomic response of skin/immune cells, when put into
contact with HS lesional flora, with different levels of immune dysregulation/deficiency, potentially leading to different phenotypes and personalized strategies (Figure 3).

8 | COMPLEMENT, COVID-19 AND HS: WHAT WE LEARN FROM THIS ASSOCIATION?

Complement split products, like complement 5a (C5a), mediate neutrophil chemotaxis and may play some role in HS pathogenesis. Indeed, C1q, C2 and factor B were found to be up-regulated and factor H, factor D and C7 downregulated in HS. C5a is produced through C5 cleavage which is mediated by C5 convertase. Activation of C5 convertase is converging towards all classical, alternative and lectin pathways. C5a was significantly increased in the plasma of patients with HS. Surprisingly, C5a was lower among patients with Hurley stage III HS than Hurley stage I, driving the hypothesis that C5a is consumed as HS worsens. Excess TNF-α was produced by the peripheral blood mononuclear cells of patients upon enrichment of growth medium with plasma; this was significantly attenuated upon addition of the selective C5a blocker IFX-1. Twelve Hurley III patients refractory to anti-TNFs were treated with IFX-1. Hidradenitis Suppurativa Clinical Response (HiSCR) was achieved in 75% at day 50 of treatment, while treatment responses were maintained three months after end of treatment in 83.3%. Remarkably, the number of draining fistulas was significantly decreased, pointing towards a role of C5a in HS fistulization.

In recent months, we have witnessed the spread of the novel coronavirus, SARS-CoV-2, which resulted in a global health emergency. COVID-19 caused by SARS-CoV-2 is associated with an acute respiratory illness that varies from mild to the acute respiratory distress syndrome (ARDS). Severe patients have complex immune dysregulation dominated either by macrophage activation syndrome or IL-6 hyperfunction. Complement activation is a common if not fixed feature of ARDS. C5a is elevated and has been proposed as a marker of ARDS associated with sepsis, cytokine storm and multiorgan dysfunction. Accumulating evidence shedding light on complement over-activation in severe COVID-19 turned attention to the therapeutic role of complement inhibitors. The PANAMO trial that investigates the efficacy of IFX-1 in severe COVID-19 is already under way. The reported beneficial responses of IFX-1 in HS generate thoughts on the C5a kinetic interplay mediating ARDS at acute activation and HS fistulization at chronic activation. At the same time, COVID-19 pandemic did not seem to affect the management of HS with biologics.

9 | TISSUE T AND B CELLS IN HS

Observational studies in moderate-to-severe HS have identified up-regulated numbers of Th1, Th17, B cells, plasma cells, monocytes,
The characteristics of cellular infiltrates in early and mild HS remain unclear. Transcriptomic studies (verified by immunohistochemistry, immune fluorescence and reverse transcription-polymerase chain reaction) demonstrate dramatic upregulation of genes associated with B and plasma cells (CD19, 25, 86, 138), T cells (CD3, 25), monocytes, dendritic cells (CD207, 303) and neutrophils.\textsuperscript{5,41} Inflammatory cell trafficking cytokines including CXCL13, IL-6 and IL-8 are consistently up-regulated in HS tissue.\textsuperscript{4,15,18,92-94} HS patients have been shown to also have autoantibodies against citrullinated and extracellular matrix proteins.\textsuperscript{93} Immunoglobulin producing plasma cells \textsuperscript{95} and B cells \textsuperscript{96} are major producers of IgD, IgG, IgM, ASCA and anti-CCP antibodies \textsuperscript{92,94,95} characterized in HS. The mechanisms of B-cell-mediated activation of other cells and potential pathogenicity are yet to be determined. Th17 cells are identified in HS lesional tissue as associated with epidermal psoriasiform hyperplasia \textsuperscript{15,18,92,94} and transepithelial neutrophil migration across tunnel epithelium.\textsuperscript{97}

Perifollicular and interfollicular mixed inflammatory cell infiltrates have been identified in the superficial dermis of mild lesions; however, these are major attractors to inflammatory infiltrates in HS, independent of lesional or perilesional status,\textsuperscript{97} different from the infiltrate found in mild disease. These observations suggest limitations to our knowledge and the importance of defining precise sample collections for mechanistic and clinical trial studies.\textsuperscript{99} The mechanistic roles of these cells also remain speculative given the rarity of reliable in vitro, ex vivo,\textsuperscript{99} and in vivo\textsuperscript{100} disease models. The interaction between cell types is an area requiring further molecular and functional investigation. The chemokine signature of HS lesional tissue and dermal inflammatory architecture is suggestive of the possibility of tertiary lymphoid organs developing in chronic HS lesions.\textsuperscript{101} This would fit with the known roles of complement, autoinflammation and autoantibody development.\textsuperscript{15,18,92,93}

Overall, the characteristics of HS lesions are well-described but their interactions and mechanistic roles in disease activity and progression remains unclear. Priorities for future research into the mechanism of T- and B-cell function in HS include translational studies utilizing targeted monoclonal antibodies and examining the role of cells in mild and early disease.

### 10 | CYTOKINES, CHEMOKINES AND HS

The excessive inflammatory response seen in lesional skin of HS is thought to be triggered by a combination of genetic, anatomical, immunological and environmental factors.\textsuperscript{94,102} Thereby cytokines play a crucial role. Several studies showed that T cells and dendritic cells are responsible for the secretion of IL-23 and IL-12, leading to a Th17 predominant immune response and keratinocyte hyperplasia.\textsuperscript{16,23,94,102} Especially IL-23 has been shown to induce IL-17 producing T-helper cells, which infiltrate the dermis in HS lesions.\textsuperscript{103} The IL-17 family of cytokines has been shown to be important in the pathogenesis of many autoimmune and autoinflammatory diseases especially also in psoriasis. IL-17 also plays an essential role in host defence against extracellular bacteria and fungi and
it has been shown to increase the expression of skin antimicrobial peptides/alarmins, such as hBD2 and psoriasin. Blocking IL-17 seems therefore a valid therapeutic approach also for HS.

During disease progression, many different cytokines have been shown to be expressed in increased levels. Especially TNF-α has been shown to be elevated. These findings resulted in the introduction of anti-TNF-α antibodies in the therapy of HS. As HS progresses, increased levels of TNF, IL-1, IL-17, S100A8, S100A9, caspase-1 and IL-10 appear in the tissue accompanied by a recruitment of neutrophils, mast cells and monocytes. Recent evidence further points to autoinflammatory mechanism in HS. HS skin shows increased formation of neutrophil extracellular traps (NET). Intriguingly, immune responses to neutrophil and NET-related antigens have been linked to enhanced immune dysregulation and inflammation. In combination with the strong type I interferon (IFN) signature in HS skin, these findings suggest a key involvement of the innate immune system in the pathogenesis of this disease.

As healing from the inflammatory process moves on, tissue scarring progresses. The development of scarring and sinus tracts is associated with metalloproteinase-2, tumor growth factor (TGF)-β and ICAM-1, with possible augmentation of TGF-β and ICAM-1 signalling via specific components of the microbiome.

### SEX HORMONES AND HS: WHAT'S NEW?

The role of hormones in HS remains to be elucidated (Figure 5). Gender predilections differ among races, as reported above. Sexual hormones and particularly androgens seem to play a role in the pathogenesis of the disease. HS related-premenstrual flares, rare postmenopausal occurrence, improvement during pregnancy, post-partum flare-ups and association of the disease with contraceptive pills with low oestrogen/progesterone ratio suggest an endocrine pathophysiology variable for the disease. A current systematic review analysed the therapeutic use of anti-androgens for HS, focusing on cyproterone acetate, spironolactone, finasteride and the antidiabetic drug metformin. The yielded case series do not provide the evidence level for wide use of hormonal treatment for HS, which remains limited to female patients with menstrual abnormalities, signs of hyperandrogenism, and/or increased serum androgens.

Obesity is one of the cardinal factors which predispose to HS and there seems to be an endocrine background fuelling a latent proinflammatory state. In a cohort study from Denmark childhood, BMI was positively and significantly associated with risk of HS development in adult age. Returning to normal weight before puberty was found to reduce risks of HS to levels of not overweight children. Insulin resistance is common in HS. Current molecular studies focus on inflammation, while the correlation with hormonal treatments might be overlooked. The antidiabetic drug metformin exhibits an anti-inflammatory effect potentially reducing IL-6, TNF-α and IL-17 through decrease of Th17 cells, Treg and suppression of the NFκB complex. Prospective and retrospective case series and case reports provide evidence for its use.

What is the window of opportunity for hormonal treatment of HS especially in the biologic era of HS? Could a major repurposing of
available hormonal medications for cutaneous diseases contribute to HS treatment?

Indeed, there are cases of HS, where patients have lost response to antibiotics and still experience frequent flares of mild disease and do not qualify for adalimumab treatment or for other upcoming biologic treatments. In such cases, hormonal treatments might provide a cost-effective alternative. Moreover, certain comorbidities, such as severe heart insufficiency, do not allow the use of anti-TNF treatment. In such cases, alternative hormonal therapies, such as the diuretic spironolactone, which has antiandrogen properties, might hold promise.

12 | CARDIOVASCULAR RISK FACTORS AND THEIR POTENTIAL CONTRIBUTION TO THE PATHOMECHANISM OF HS

There is strong epidemiologic evidence that cardiovascular risk factors appear at a significantly higher rate in HS patients as compared to healthy individuals. Among those risk factors, which are also commonly associated with metabolic syndrome, are obesity and in particular central obesity, insulin resistance, diabetes and dyslipidaemia, as already highlighted above (Figure 5). HS is significantly related to presence of carotid plaques and increased frequency of subclinical atherosclerosis and is associated with a significantly increased risk of adverse cardiovascular outcomes and all-cause mortality independent of measured confounders. Notably, the risk of cardiovascular death is 58% higher in patients with HS than in patients with severe psoriasis. Obesity affects the overall morbidity and prognosis of patients with HS and weight reduction can have a beneficial effect on HS prevalence and severity and even lead to spontaneous resolution of disease. Obesity elicits a low-grade systemic inflammation caused by adipocytes that secrete metabolically active proinflammatory mediators known as adipokines. The secretion of adipokines has been found to be dysregulated in HS. These propagate the inflammatory cascade by recruiting macrophages to the adipose tissue, which release further proinflammatory mediators. In this regard, it has been reported that the adipokines resistin and leptin were found increased in patients’ serum and adiponectin was decreased.

High systemic inflammatory burden may cause a state of insulin resistance in inflamed tissues which is causally linked to endothelial dysfunction and atherosclerosis. As a result, reduced adiponectin and increased resistin serum levels have been identified as surrogate biomarkers for insulin resistance in patients with HS. Resistin and visfatin were proposed to be involved in HS pathogenesis. Moreover, nutritional excess in metabolic syndrome can lead to adipose tissue expansion and adipocyte hypertrophy associated with increased release of inflammatory mediators. In subcutaneous adipose tissue, this can cause cutaneous inflammatory responses but also spill-over of inflammatory mediators into the systemic circulation contributing to progression of the metabolic syndrome.

Among the inflammatory mediators produced by adipocytes are arachidonic acid-derived polyunsaturated fatty acids (PUFAs) of the ω6 class, the so-called eicosanoids. High-fat diet and in particular western diet containing a high ω6/ω3 ratio can further enhance the release of arachidonic acid-derived lipid mediators by adipocytes. Adipocytes are among the few non-leucocyte cell types that possess the enzymatic machinery to produce the proinflammatory eicosanoid leukotriene B4 (LTB4), which confers not only macrophage and neutrophil infiltration and activation but also contributes to insulin resistance and has been implicated with increased cardiovascular risk. Interestingly, comprehensive PUFAs lipidomics analysis of HS skin lesions has recently identified LTB4 as the most dominantly up-regulated proinflammatory lipid mediator in HS lesions, produced mainly by lesional macrophages. The potential contribution of proinflammatory LTB4 to dysregulated innate immunity in HS is currently investigated in clinical trials, and it is tempting to speculate that elevated levels of this inflammatory mediator may also contribute to metabolic syndrome-associated comorbidities in HS.

13 | SMOKING AND HS

HS is a tobacco-related skin disease. The role and mechanisms of cigarette smoke (CS) in HS remain speculative. CS is composed of numerous chemicals, whereas nicotine, benzopyrenes and dioxin-like compounds are the most well-known.

The natural ligands of nicotine are the nicotinic acetylcholine receptors (nAChRs), which are identified in skin keratinocytes, sebocytes and immune cells constituting the non-neuronal cholinergic system. Many HS patients are heavy smokers, since they use tobacco to alleviate symptoms of anxiety and depression. Variability in genes that encode nAChR subunits is associated with multiple smoking phenotypes and could explain a certain profile of HS smokers. Nicotine negatively impacts keratinocyte functions, including the stimulation of chemotaxis, cytokine release and oxidative stress and also stimulates keratinocyte differentiation and epithelial hyperplasia. In epidermis of patients with HS, there is a strong expression of nAChR around the pilosebaceous unit leading to infundibular epithelial hyperplasia and follicular plugging. Furthermore, studies have revealed highly potent effects of the cholinergic system on sebocyte proliferation and lipid production in vitro, but the role in HS is unclear.

In addition, CS appears to further stimulate the dysbiosis-driven aberrant activation of the innate immune system in HS. Nicotine, as an alkaloid, appears to promote growth of Staphylococcus aureus, thus modifying the microbiome and inhibits the synthesis of antimicrobial peptides, such as hBD2, rendering the follicle more susceptible to bacterial invasion.

Smokers in comparison with non-smokers exhibit higher serum levels of proinflammatory cytokines and TNF-α. Human bronchial epithelial cells release IL-1β and express caspase-1 via stimulation of Toll-like receptors, after incubation with CS. In mouse models,
Nicotine was found to activate NLP3 inflammasome.\textsuperscript{165} Smoking adversely affects the Th17/Treg balance. It has been associated with increased expression of Th17 cells, IL-17 expression and impaired numbers or function of Tregs.\textsuperscript{150} Furthermore, downregulation of Notch pathway gene expression has been reported in association with smoking.\textsuperscript{155}

Finally, dioxin-like compounds and benzopyrenes of CS trigger in vivo and in vitro the aryl hydrocarbon pathway which is present on keratinocytes, sebocytes and immune cells.\textsuperscript{152,153} Exposure to extremely high concentrations of dioxins induces hyperkeratinization of the pilosebaceous unit and a metaplastic response of the sebaceous glands producing clinical lesions of chloracne.\textsuperscript{154} whose clinical features are highly similar to the "smokers' boils" in HS.\textsuperscript{155} The possible actions of CS in HS are summarized in Figure 6.

\textbf{14 | HAIR FOLLICLE STEM CELL REPLICATION DISORDER VS. ALOPECIA AREATA COMORBIDITY VS APOCRINE GLAND DISEASE: WHERE IS THE EVIDENCE?}

From its naming, the apocrine gland was implicated as a major contributor in HS pathogenesis. In contrast, histopathologic and molecular studies indicate significant involvement of the hair follicle with secondary apocrine gland injury.\textsuperscript{156-159} There are a number of changes in the hair follicle including an occluding spongiform inflammation in the infundibulum with predominantly T cells and infundibular disintegration in early lesions.\textsuperscript{157,160} Hair follicle keratinocytes also produce more proinflammatory cytokines and have an altered pattern of antimicrobial peptide production.\textsuperscript{15} Impaired hair follicular stem cells (hfSCs) homeostasis leading to an increased proliferation induces stress replication and stimulates type I IFN production which participates to the strong inflammatory skin reaction.\textsuperscript{161} Dysregulation of the T reg/Th17 axis may also impact hfSCs and subsequently lead to structural instability of the infundibulum.\textsuperscript{95,162} Thus, the follicle cells are altered towards a proinflammatory state that may underlie follicular instability and promote the inflammatory response.

HS pathogenesis involves both hair follicle disruption and a robust immune response.\textsuperscript{162} however, the hfSCs at the bulge are immune privileged, lacking MHC I expression. It is theorized that alopecia areata (AA) is caused by the loss of immune privilege at the hair follicle either due to disruption of the hair follicle epithelium or a dysregulated immune response.\textsuperscript{164,165} HS has been associated with multiple inflammatory and autoimmune diseases, including AA.\textsuperscript{166,167} In a Korean study, AA was more common in patients with HS than in patients without HS (adjusted odds ratio = 1.35).\textsuperscript{166} Similarly, AA was also more common in patients with HS (adjusted odds ratio = 1.99) in a US study.\textsuperscript{168} The lesions of HS and AA have considerable overlap in inflammatory cytokines, including TNF-\(\alpha\), IL-17, IFNs, chemokine ligands 9 and 10, granzyme B, and others.\textsuperscript{43,164} It is not known yet if inflammatory phenotype of hfSC in HS leads to the loss of hair follicle progenitor cells promoting AA; however, investigating the association between these two diseases may help elucidate the pathogenesis of each.

\textbf{15 | WHAT WE LEARN FROM “ECTOPIC” AND “SYNDROMIC” HS?}

Recent attempts to classify HS phenotypes have distinguished “typical” and “atypical” HS;\textsuperscript{169} syndromic and ectopic HS belong to the latter. Autoinflammatory syndromes associated with HS and/or acne are rare.\textsuperscript{170} Their common pathogenic feature is an over-activation of innate immunity with aberrant activation of IL-1 and IL-17/TNF-\(\alpha\) axis resulting in the formation of neutrophilic infiltrate.\textsuperscript{171} The onset of HS as part of their skin involvement raised the hypothesis to reconsider HS as a Th17-driven autoinflammatory disease. Interestingly, mutations in \textit{PSTPIP1} gene, that encodes for components of the inflammasome, a cytosolic multiprotein oligomers responsible for the IL-1 synthesis have been described in 2 forms of syndromic HS,\textsuperscript{19} the PASH syndrome\textsuperscript{19,20,172} and the PAPASH syndrome defined by the PASH triad of pyoderma gangrenosum, acne
and HS and the presence of pyogenic arthritis.\textsuperscript{173} The addition of either spondylarthritis (PASS)\textsuperscript{174} or psoriatic arthritis (PsAPASH)\textsuperscript{175} to the triad has also been described but associated mutations are not identified. It is crucial to increase the awareness about syndromic HS and the use of drugs that target IL1-TNF-α/IL-17 may represent attractive therapeutic options.\textsuperscript{176}

In opposite, ectopic forms of HS do not develop regarding typical intertriginous and apocrine gland-bearing skin areas and may affect convex and/or apocrine gland-free areas (ear, chest, neck, nape, leg). Local mechanical stress represents the main triggering factor\textsuperscript{177,178} including friction, shearing and pressure. Mechanical follicular occlusion could be a mechanism by which local trauma would promote HS onset and molecular signalling underlying mechano-transduction should be explored. Interestingly, γ-secretase mutations causing impaired Notch pathway and thereby promoting Th17-driven inflammation have been reported in small numbers of HS cases.\textsuperscript{26} Whether mechanical-induced alterations in the Notch pathway could also result in apocrine metaplasia of eccrine glands could be discussed,\textsuperscript{179} since Notch has been identified as a regulator of skin stem cells fate.\textsuperscript{180}

16 | HOW ITCH AND PAIN OCCUR IN HS?

It is obvious that pain accompanies HS, as the vast majority (95.2%-97.1\%) of patients, report it during the disease course.\textsuperscript{181,182} It is perceived as the most troublesome symptom of HS.\textsuperscript{181} Although one decade ago HS was not considered a pruritic disease, itch is also a common HS-associated symptom (62.1%-77.5\% of reporting patients) that adversely affects patients’ quality of life.\textsuperscript{181-183} Of note, the co-occurrence rate of pain and itch in one location was surprisingly high, as reported by 59.5%-74.9\% of patients.\textsuperscript{181,182}

It could be assumed that both, acute pain observed during flare-ups and itch frequently reported in the initial phase of HS (as a prodrome) have a nociceptive character, linked to the local activation of cells of the innate and adaptive immune systems, with pivotal roles for proinflammatory cytokines and various chemokines, which can bind directly to their specific receptors on the peripheral terminals of the afferent nociceptive neurons.\textsuperscript{9,184-187} The unrestricted and chronic immune response observed in HS leads to pyroptosis resulting in irreversible tissue destruction and scar development. This could alter the character of subjective symptoms and lead to the development of neuropathic pain and/or itch being a consequence of the nervous system structures damage, or sometimes of prolonged, unremitting nerve stimulation. Neuropathic pain and itch are often associated with each other, and hypersensitization to stimuli is present in both pain and itch of neuropathic origin.\textsuperscript{188} Recent considerations regarding chronic pain in HS tried to explain this phenomenon through the process of central sensitization, which is the effect of first-order afferent nociceptive neuron repeated and increased activation during chronic and recurrent inflammation.\textsuperscript{189} HS may promote the central sensitization development through its highly expressed systemic inflammatory burden. Soluble TNF-α receptor, IL-6, IL-17 and IL-23 have been found to increase the blood-brain and blood-spinal cord barrier permeability, potentially aiding the infiltration of immune cells and inflammatory mediators into the central nervous system.\textsuperscript{190} Here, these inflammatory cytokines may influence synaptic transmission analogous to locally released cytokines.\textsuperscript{185,187,189} Therefore, not only analgesics or selective serotonin reuptake inhibitors, but also anti-inflammatory/immunomodulating therapies, could play an important role and significantly alleviate the intensity of pain and itch sensation.\textsuperscript{191}

17 | PATHOGENESIS-ASSOCIATED FUTURE THERAPIES

Our modern understanding of the pathogenetic pathways that drive hidradenitis suppurativa is rapidly emerging. New tools that allow the characterization of the microbiome, proteome and transcriptome are opening up new avenues of investigation.\textsuperscript{192} But perhaps most interesting is the in vivo exploration of new targeted immunologic therapies. The use of new agents is likely to accelerate our understanding as they present the opportunity to use clinical effectiveness to validate relevant patterns. Indeed, the pathogenetic patterns of HS are likely to be elucidated from bedside to bench, even as they are from bench to bedside. Conducting inclusive, long-term, controlled multi-centre clinical trials investigating different biological agents or drugs with ancillary analyses of transcriptomes will leap forward the HS patient journey. These will build the foundations to fully integrate our HS transcriptome knowledge with clinical records, epidemiologic and demographic factors.\textsuperscript{98}

To date, however, HS remains a “messy” immunologic disease. Many cytokines have been identified in histologic samples, but the sequence of the pattern and the key initiators are still a work in progress. A recent paper by Frew et al\textsuperscript{65} demonstrated no consistent cytokine patterns. However, the inhibition of TNF-α, IL-1 and IL-17 has been validated in clinical trials as relevant. Other transcriptomic studies have reaffirmed their role and have additionally suggested that androgen receptor, interferon-γ, IL-6, Growth Arrest-Specific 6, Glial Cell-Derived Neurotrophic Factor and Hepatocyte Growth Factor are viable targets using currently available agents (Table 1). There is also early data suggesting that IL-23, C5a and Janus kinase inhibitors may be successful targets.

As both targeted and multimodality approaches are tested, it will be interesting to see whether, given the high inflammatory load, a multimodality approach is more effective for induction, and more targeted approaches are useful for maintenance. Generally, effective treatment of HS with targeted anti-TNF agents has required higher doses than other skin diseases even with weight-based dosing.\textsuperscript{193,194} Moreover, the cytokine profile of lesional skin suggests tamping down other parts of the inflammatory cascade simultaneously could be useful. In any event, the number of effective agents currently under study is enormously encouraging and will lead us to better understand the disease and help our patients.
18 | WHAT ARE WE EXPECTING IN THE FUTURE?

Although a huge amount of knowledge has accumulated in the last 15 years, including simplified diagnostic criteria for early recognition of the disease, we are just at the beginning of understanding HS and being able to treat it effectively. Future targets are emerging. Highly sophisticated molecular studies, such as next generation sequencing analyses, will further increase the molecular understanding of HS aetiology, which already has a solid basis due to current relevant studies. Through such reports, a clearer association of different clinical phenotypes with relevant molecular expression patterns may be recognized, which will fulfill the requirements of personalized medicine in HS. Clinical and laboratory biomarkers may accompany improved clinical outcome measures for better monitoring of the disease course. Robust ex vivo models might corroborate clinical data. Clearer documentation and newer diagnostic techniques, such as standardized photography, ultrasound and thermography, together with apps for prospective evaluation of relevant patient outcome measures, such as daily assessment of pain, may lead towards the digitalization and objectification of clinical follow-up. Ultimately, successful early HS treatment will aim to spare HS patients from progression of the disease and preventing large surgical excisions, complications and recurrence.

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CONFLICT OF INTEREST

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