Pathophysiology of hidradenitis suppurativa

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Abstract

The pathophysiology of hidradenitis suppurativa (HS) is not well understood. Some of our knowledge comes from clinical and epidemiological observations, along with studies of the histopathology and immunohistochemistry of affected skin. More recently, cutaneous molecular studies and transcriptomic analyses have provided additional information regarding inflammatory processes. The chronic cutaneous inflammation, systemic symptoms, and associated comorbidities suggest that HS should be classified as an immune-mediated disease, rather than a primary infectious disease. As such, a proposed integrated disease pathway is presented. At a fundamental level, there appears to be a primary abnormality in the pilosebaceous-apocrine unit, which leads to follicular occlusion, perifollicular cyst development that traps commensal microbes, and rupture into the dermis. This can trigger an exaggerated response of the cutaneous innate immune system. Initially this is an acute event, but ongoing intermittent disease activity can lead to recurrent inflammatory nodules and dermal tunnels. Once underway, the cutaneous inflammation is very difficult to turn off, leading to suppurative inflammation in whole anatomic regions. As the disease progresses, we propose that there is recruitment of the systemic immune system perpetuating the chronic cutaneous inflammatory process. There remains much to be done to understand the pathogenesis and immune signature of this challenging disease.

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Examining the clinical features, natural history and epidemiology, histology, and microbiology of diseased tissues can give clues to potential causes of hidradenitis suppurativa (HS). Investigations into the cutaneous and systemic immune system to date suggest a role for a dysregulated immune response. However, the key pathogenic pathways in HS have not yet been elucidated. An integrated model of pathophysiology will be presented that considers possible abnormalities of the pilosebaceous-apocrine unit leading to an exaggerated immune response that may drive disease progression.

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Clinical features and natural history of HS

The clinical course of an individual inflammatory HS nodule is well characterized. Typical acute lesions present as very painful erythematous nodules in the axilla and/or groin that can come up quickly, sometimes with associated fever.[1] The nodules may "pop," leaking a bloody suppurative odiferous discharge, and the areas heal with atrophic scarring. The average duration of an acute HS lesion is 6.9 days. Inflammation appears to be deep in the dermis as lesions are not usually pustular or acneiform. The frequency of these lesions can vary, with a median of 2 abscesses per month (mean 4.6 per month), and 62% of patients described persistent painful inflammatory lesions. As the disease progresses, the lesions may become more frequent. The inflammatory nodules may burst into the dermis and form palpable cords and suppurative dermal tunnels.

In contrast, disease progression in HS is not as well characterized, and it is not known what conditions predispose to progression. HS disease severity can be classified using the Hurley staging system.[2] Persistent inflammation results in nodules and dermal tunnels, constant suppuration, and hypertrophic scarring in whole anatomical regions. Large open comedones, often double-headed, are indicative of follicular obstruction. HS has a large disease burden encompassing not only the cutaneous manifestations, but also other comorbidities and disease associations,[3-5] described in Figure 1.

Epidemiological observations

The female to male ratio in HS individuals is consistently reported around 3 to 1.[3] HS commonly presents at the time of menarche and some female patients report flares with their menstrual cycle, which suggests that hormones have a prominent role in HS pathogenesis. However, there have not been consistent abnormalities detected in circulating hormones, with most studies showing no biologically meaningful differences.[5] Hence, this effect may be due to increased hormonal sensitivity of apocrine glands.

While HS is not a classic infection, bacteria are an agent in disease progression. Patients rarely present with lymphangitis, infectious cellulitis, or tender regional lymphadenopathy. An ultrasound study showed that lymph nodes in chronic HS regions were only slightly enlarged, suggesting minor dermatopathic inflammation associated with HS lesions.[6] Furthermore, bacterial cultures of HS lesions mostly reveal normal skin commensals, mainly coagulase-negative *Staphylococcal* species, *Corynebacterium* species, and anaerobes.[7] Additionally, bacteria in HS may form a biofilm, where a type of capsule protects the bacteria and allows them to persist.[8] Antibiotics are mainly used as treatment to decrease bacterial load and as anti-inflammatory agents, rather than for their traditional antibacterial mechanism of action.

In most epidemiological studies of HS, there is an association with cigarette smoking (up to 90% of patients have smoked

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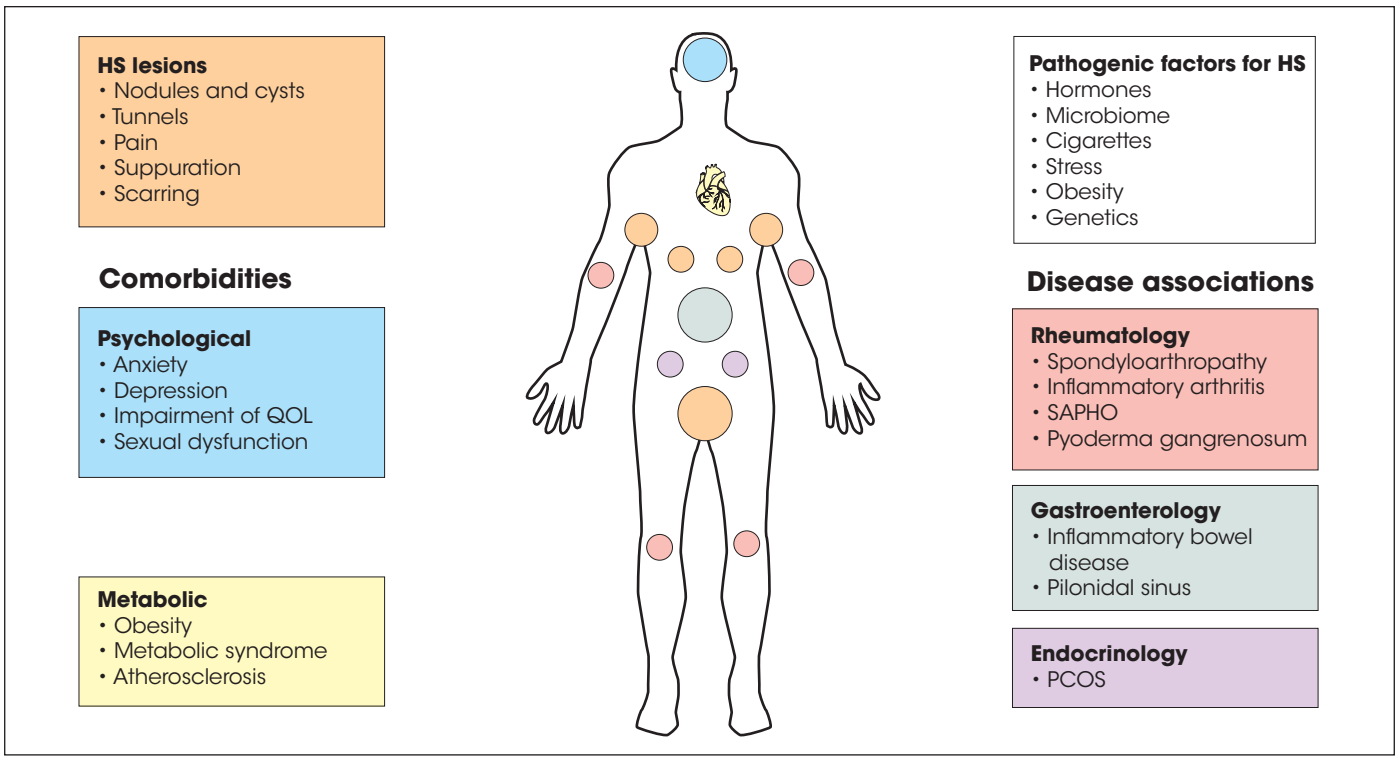

FIGURE 1. The burden of HS disease. Characteristic HS lesions include painful inflammatory nodules and cysts, suppurative dermal tunnels, and scarring in the axilla and groin. Pathogenic factors suggested by epidemiology include hormones, the cutaneous microbiome, cigarette smoking, stress, obesity, and genetics. There are significant psychological comorbidities. There are associations between HS and the metabolic syndrome, a disorder associated with obesity, hypertension, hypertriclyceridemia, low HDL, and diabetes. Other rheumatologic, gastroenterologic, and endocrine diseases have been reported to occur in the setting of HS. The follicular occlusion tetrad encompasses HS, dissecting cellulitis, acne conglobata, and pilonidal sinus.

Abbreviations: HDL, high-density lipoprotein; HS, hidradenitis suppurativa; PCOS, polycystic ovary syndrome; QOL, quality of life; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome.

tobacco).[9] Exactly how cigarettes contribute to HS pathogenesis remains undetermined. Nicotine receptors are strongly expressed on follicular epithelium.[10] Nicotine causes effects that could be pathogenic in HS, including neutrophil chemotaxis, cytokine (TNF) production by keratinocytes, stimulation of *Staph aureus*, induction of epidermal hyperplasia, and down regulation of antimicrobial peptides (AMPs) such as beta-defensin.[11] There may also be alternative pathogenic compounds in cigarette smoke, such as polyaromatic hydrocarbons or dioxin-like compounds, which may bind to immunomodulatory aryl hydrocarbon receptors.[12] However, anecdotal reports suggest smoking cessation does not always resolve disease activity, perhaps due to the multiple risk factors and comorbidities associated with HS.

Obesity is also commonly associated with HS, and may contribute to disease pathogenesis in several ways. Obesity may enhance mechanical friction in the axilla and groin which promotes follicular occlusion. In addition, obesity is now considered to be its own state of inflammation.[13] Adipocytes can release pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin (IL)-6, which could contribute to the systemic inflammation associated with HS.

"Stress," a complicated factor to measure, is reported to exacerbate HS. The dermatology life quality index (DLQI) questionnaire is the assessment tool that has been most commonly used to capture the psychological impact of HS. Several studies have shown a very high DLQI score for HS, similar to other severe chronic skin diseases.[3] Apocrine secretions are sometimes called stress or emotional sweating.[14] As nervous innervation or cholinergic receptors were not identified on or near apocrine glands,[15] it is more likely that the glands are responding to circulating adrenergic mediators.

A third of patients with HS report a positive family history of HS, and genetic studies have indicated an autosomal dominant mode of inheritance. Mutations were identified in the genes of the *gamma-secretase* complex and HS patients with this mutation have a more extensive clinical phenotype.[16] The potential role of this mutation is discussed further below. An additional HS genetic susceptibility factor was carriage of more than 6 copies of the *beta-defensin* cluster, which may also drive a more severe clinical phenotype.[17]

Characterization of HS lesional skin

Careful histopathological examination of HS lesional biopsies has revealed that early events in lesion development include follicular hyperkeratosis and hyperplasia at the infundibulum (Figure 2), follicular occlusion, and lymphocytic perifolliculitis.[18,19] As inflammation was not seen around all apocrine glands, apocrinitis has come to be viewed as a secondary rather than a primary pathological event. There appears to be fewer and smaller sebaceous glands in the perilesional skin of HS patients as compared to healthy controls,[20] which may be a consequence rather than related to disease pathogenesis.

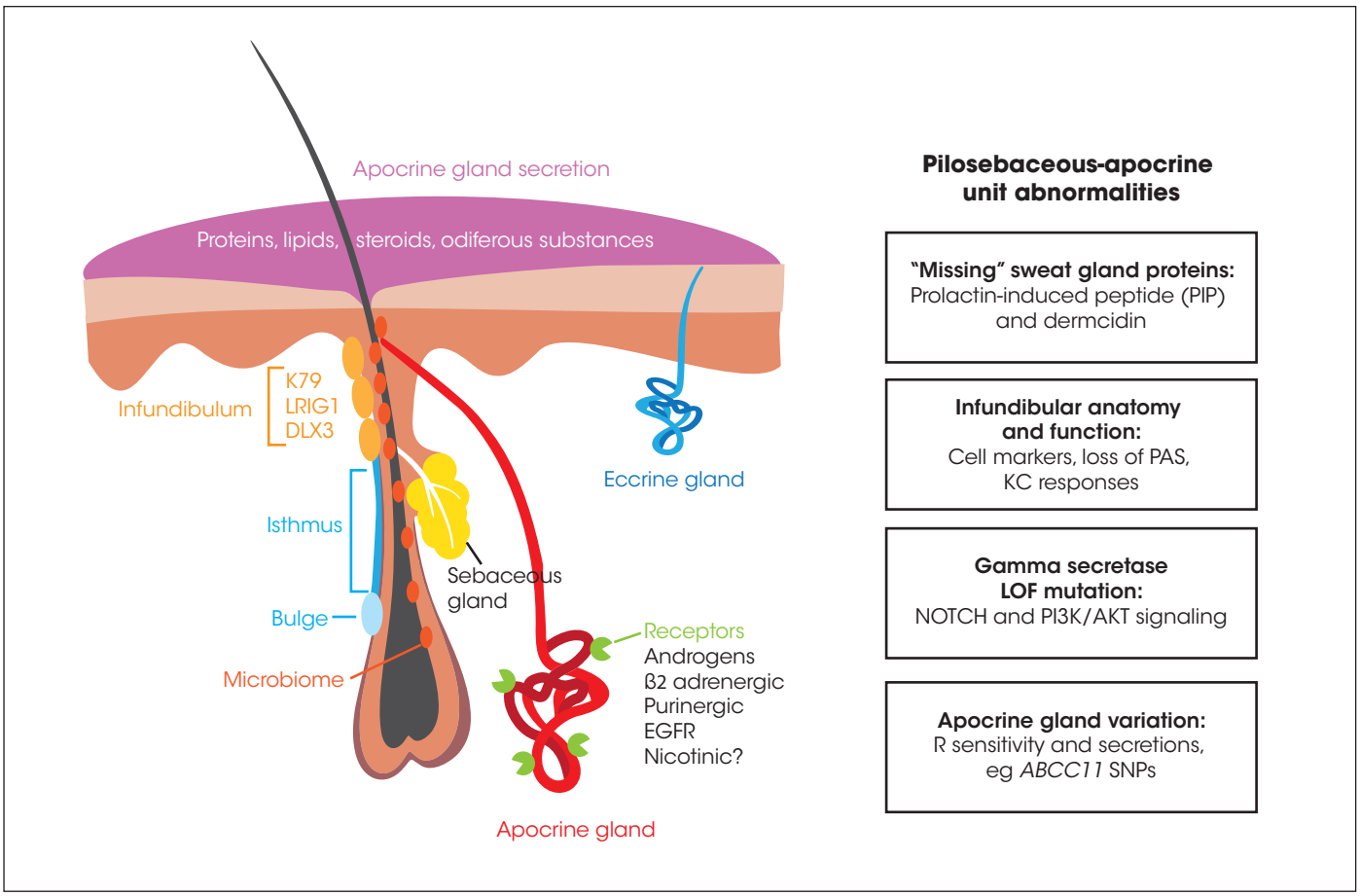

FIGURE 2. Pilosebaceous-apocrine unit. There are two main kinds of sweat glands in human skin. The more numerous eccrine glands produce electrolyte-containing watery sweat for temperature control. The eccrine duct drains via the interfollicular epidermis through a specialized coiled structure called the acrosyringium. In comparison, the apocrine glands arise as part of the pilosebaceous unit. The permanent portion of the hair follicle is composed of the upper infundibulum, isthmus, and bulge of undifferentiated keratinocyte stem cells, and these regions can be identified by various markers. Apocrine glands are mainly found in terminal hair-bearing skin in the axilla and groin. Apocrine units can also be found in the peri-umbilical, perineal, and perianal regions, prepuce, scrotum, mons pubis, labia minora, areola, external auditory canal (ceruminous glands), and on the eyelids (Moll's glands). The apocrine glands are larger and deeper in the dermis, and secretion occurs by pinching off a portion of the outer cell membrane, termed decapitation secretion. The apocrine gland drains via a straight dermal duct which passes through the hair follicle infundibulum by a coiled acrosyringium just above the sebaceous gland. Apocrine glands possess numerous receptors for local and circulating mediators. Once produced, apocrine sweat is degraded by commensal bacteria to generate odiferous substances. Boxes on the right of figure indicate potential pathogenic abnormalities of the pilosebaceous-apocrine unit discussed in the text.
Abbreviations: EGFR, epidermal growth factor receptor; KC, keratinocytes.

Immunohistochemistry has revealed the presence of many chronic inflammatory cells in lesional skin, including neutrophils (neutrophil elastase), T cells (CD3), B cells (CD19, CD20), plasma cells (CD138), NK cells (CD56), mast cells, macrophages (Factor XIIIA, CD68), and dendritic cells (CD11c, CD14).[21,22] Multinucleate giant cells and foreign body granulomas have also been identified in HS excisional tissues.[23]

Dermal tunnels are a specific feature of advanced HS, and studies of lesional tissue suggest that these may originate from the epidermis. "Fingers" of proliferating (Ki67+) keratinocytes appear to probe down from the proliferative epidermal hyperplasia into the dermis and this may lead to tunnel formation.[24] Increased MMP1, MMP2, and MMP8[25-27] may provide a proteolytic mechanism for tunnel formation. Pathological stratified squamous epithelium has been identified in draining "sinuses" of HS.[28] Epithelialization of the tunnels may explain the persistence of these structures and the difficulty treating them medically.

Contribution of the immune system

Data to date suggest that there is immune dysregulation in both the cutaneous and systemic immune system in patients with HS, but relative contributions from the innate and adaptive immune systems have not been fully elucidated.

Abundant evidence suggests activation of the innate cutaneous immune system in HS.[29] There is a mixed inflammatory cellular infiltrate and inflammasome activation in HS epidermis,[22,30] and keratin filaments found ectopically in the dermis may stimulate the inflammasome.[24] AMPs, a first line of defense against bacteria by activation of pattern recognition receptors, have been shown to be variably altered in HS, including LL37/cathelicidin as well as beta-

defensins and S100 proteins.[22,26,31-34] Toll-like receptor (TLR) 2 was increased in HS,[21] but TLR-3,-4,-7,-9 were decreased compared to non-lesional skin.[35]

A number of studies evaluated key inflammatory cytokine expression (either mRNA or protein) in lesional HS skin compared to healthy control skin, tabulated in a recent review by Kelly et al.[29] In summary, cytokines consistently shown to be increased in lesional skin include TNFa, IL-1b, IL-8, IL-10, IL-17, IL-20, IL-22, and IL-23.[25,26,30,32,33,36-38] In different studies, interferon gamma (IFNG) was both increased and decreased.[32,37,38]

There were also abundant inflammatory cytokines in the HS suppurative discharge.[39] In-vitro stimulated HS follicular keratinocytes secreted more IL-1b, IP-10, RANTES, and a specific pattern of AMPs.[38] Inflammation-related micro-RNAs were also altered in HS.[40,41] Peri-lesional and lesional skin of patients with HS showed increased IL-17- and IFNG-producing CD4+ T cells, but not IL-22 secreting T cells.[22,30,38]

Cutaneous transcriptomics of lesional HS biopsies have revealed many upregulated immunoglobulin gene transcripts, as well as S100 proteins (S100A7/psoriasin, S100A8, S100A9), and AMPs (DEFB4A).[42] The highest upregulated cytokines were CCL18 and CXCL1. Other notable upregulated genes included SERPINB3 and B4, ADAMDEC1, ADAM12, TDO2, TCN1, MMP12, and GZMB. Ingenuity pathway analysis revealed highly expressed pathways included *Granulocyte* and *Agranulocyte Adhesion and Diapedesis*, *Atherosclerosis Signaling*, and *Primary Immunodeficiency Signaling*. A second transcriptomic analysis revealed pathways that were closer to psoriasis, with the top pathways being *Role of IL-17A in Psoriasis* and *Interferon Signaling*.[38] These differences could be explained by the sample source, as the first study compared the transcriptome of lesional to paired nonlesional skin, whereas the second study compared lesional HS skin versus normal skin.

The systemic immune system has not been well characterized in HS. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated in most reported studies.[43] IgE has also been shown to be elevated.[44] An early effort to measure common pro-inflammatory cytokines in serum of HS patients showed that only IL-6 was elevated.[45] Serum TNF and IL-17 have been shown to be elevated in larger cohorts of patients with HS,[46,47] but not in a smaller study.[48]

A recent serum proteomic study revealed 54 proteins were significantly differentially expressed in the sera of HS patients, and the top 4 upregulated proteins were LTA4H, FSH, LH, and HCG.[48] Stimulated monocytes from patients with HS produced less cytokines than healthy controls, which could be a primary abnormality or due to exhausted cells,[39] although this has not been seen in all studies of monocyte function.[38] There were increased IL-17A+ and IL-22+ circulating CD4+ T cells in patients with HS, but not CD4+IFNG+T cells.[38] In two small studies analyzing the transcriptome of peripheral blood mononuclear cells, HS patients did not show any differences compared to healthy volunteers.[38,42] The limited evidence thus far reinforces the need to further study the cellular and humoral immune system in HS patients and how it relates to disease manifestation.

Anti-cytokine treatment studies have not yet revealed the primary cytokine signature in HS. To date, there have been clinical trials with anti-TNF, anti-IL-1 and anti-IL-23 agents.[48-51] Adalimumab demonstrated a 50% reduction of inflammatory nodules in approximately 45% of moderate to severe patients,[51] suggesting that TNF is an important inflammatory mediator in HS. Anti-IL-1 and anti-IL-23 biologics showed improvement in a subset of patients.[48,50] As there are differential responses to these biologics, there is likely to be a role for personalized medicine in treating HS.

A proposed integrated disease pathway

Given the episodic nature of early HS lesions and progression in some patients to more severe disease, there is likely an acute cutaneous initiation phase which becomes a chronic inflammatory phase. However, it is not yet clear how the disease starts or progresses. Building on earlier pathogenic models,[12,29] it is proposed that HS has primary pathogenic components in the pilosebaceous-apocrine unit. This results in subclinical follicular occlusion with continued apocrine gland secretion leading to perifollicular cyst formation and trapping of commensal bacteria. There is eventual cyst rupture into the dermis and activation of the innate cutaneous immune system. Once inflammation has begun, it is very difficult to turn off in some patients, with subsequent recruitment of the systemic immune system.

As HS presents in areas of apocrine gland-bearing skin, it is important to review the biology of the pilosebaceous-apocrine unit, which is diagramed and described in more detail in Figure 2. At the level of the pilosebaceous-apocrine unit, several nonmutually exclusive concepts will be discussed that could predispose to initiation of HS lesions (Figures 2 and 3).

Gamma-secretase LOF mutations

Gamma-secretase is a multiscaffold protein complex responsible for intra-membrane protein cleavage of many substrates.[52] The *nicastrin* subunit of *gamma-secretase* was most commonly mutated in HS, leading to loss of function.[16,53] In vitro knock down of *nicastrin* regulates keratinocyte proliferation and differentiation mainly through the Notch and PI3K/AKT signaling pathways.[54] Notch signaling is important in epidermal and appendage development and for healthy immune function. A mouse model with *gamma secretase* genetic knockout showed several features of HS skin with infundibular plugging, cyst formation, and disappearance of sebaceous glands.[55] However, inflammation, abscess formation, fistulae, and scarring were absent. Murine *Notch* knockouts were similar to *gamma-secretase* knockouts, but without infundibular plugging.[56] As mice do not have apocrine glands, these models are interesting, but they are not completely relevant to HS disease in humans. Current in vitro and model systems do not support that deficient Notch signaling is a complete explanation for *gamma-secretase* mutations.[57,58] Hence, there could be important gamma-secretase substrates to consider other than Notch. In addition, *gamma-secretase* mutations are not likely to fully explain pathogenesis as they are not present in all patients with HS.

Apocrine gland variation

A variation in any of the features of apocrine glands, such as embryology, receptor sensitivity, and secretions, might contribute to disease pathogenesis.[59,60] Although stimuli for apocrine secretion are not well defined, these glands possess androgen receptors,[61] beta-adrenergic receptors, purinoreceptors,[15] epidermal growth factor (EGF) receptors,[62] and weakly express receptors for estrogen.[61] Apocrine sweat primarily consists of proteins, lipids, and

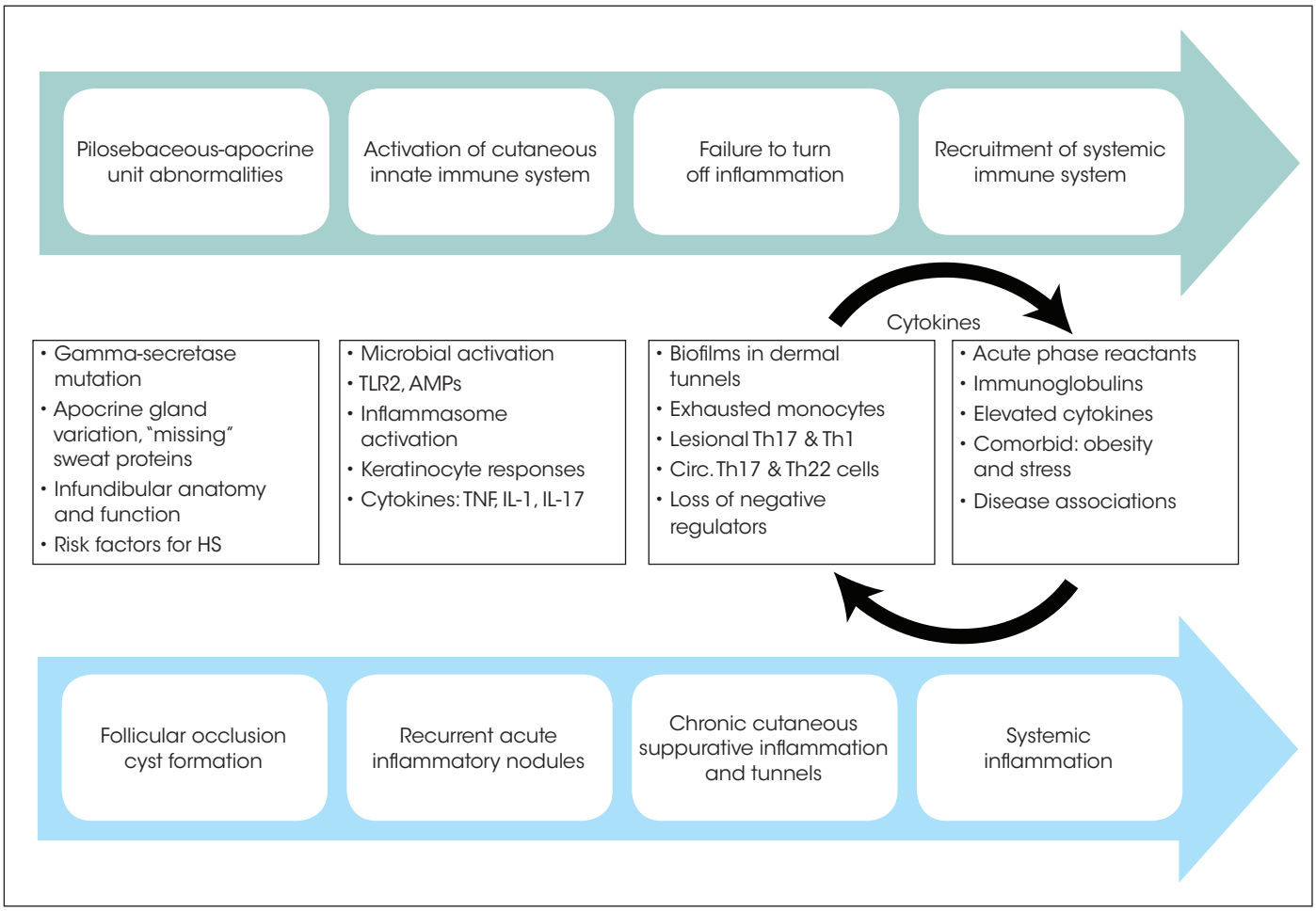

FIGURE 3. Proposed pathogenic model of hidradenitis suppurativa (HS). At the level of the pilosebaceous-apocrine unit, there are numerous possible abnormalities that could alter apocrine gland structure and/or function, modified by risk factors such as obesity, cigarette smoking and stress. These factors together could initiate hair follicle occlusion, accumulation of apocrine gland secretions in perifollicular cysts, and dermal rupture. These different initiating factors may lead to a final common pathway of HS lesion development, and could be responsible for different clinical phenotypes. The cutaneous innate immune system is initially engaged by several mechanisms, including dermal commensal microbes activating TLR2 via lipoproteins, inflammasome activation, and follicular keratinocyte responses. The immune system activation then causes the release of antimicrobial peptides (AMPs) and cytokines such as TNF, IL-1b, and IL-17. This leads to acute cutaneous inflammation with recurrent painful erythematous nodules. When usual mechanisms fail to restore homeostasis, chronic inflammation can develop with persistent cutaneous suppurative discharge and dermal tunnels. Possible mechanisms include the presence of biofilms in epithelialized dermal tunnels, exhausted monocytes, increased Th17 cells, and possibly loss of negative regulators. The systemic immune system is recruited as inflammation persists during HS disease progression, as shown by the presence of acute phase reactants, immunoglobulins, elevated cytokines, as well as HS comorbidities and other disease associations. While the immune/cytokine signature of HS is not yet determined, IL-6 may play a role in driving some of these systemic features.

steroids in an oily but odorless substance.[14,59,63] The apocrine sweat products are degraded by commensal bacteria in the microbiome of the hair follicle, including *Corynebacterium* species, to produce odiferous substances such as 3-Methyl-3-sulfanylhexan-1-ol.[64]

Volume and composition of apocrine secretion may be genetically determined by the *ABCC11* gene.[65] This gene is inherited in a Mendelian fashion and can be used to trace migration patterns. An important single nucleotide polymorphism (SNP) at 538 determines "wet" earwax and body odor (GG [homozygous dominant] or AG), while the recessive AA genotype determines "dry" earwax and lack of body odor. This recessive AA genotype at SNP538 is seen predominantly in Asians. The functional consequences of the recessive AA genotype appear to be that the ABCC11 protein produced is targeted for ubiquination and proteasomal degradation, rather than being able to process the apocrine gland substrate. It is tempting to speculate that the recessive AA genotype is protective for HS, and this warrants further investigation.

"Missing" sweat gland proteins

The top 2 down-regulated genes in lesional versus nonlesional transcriptomic analysis of HS skin were prolactin-induced protein (PIP) and dermicidin.[42] Prolactin-induced protein is an aspartic peptidase found in the epidermis and acrosyrinx of eccrine sweat glands.[66] Application of prolactin-induced protein to a 3D human skin model caused digestion of stratum corneum and epidermal proliferation. Dermcidin, or proteolysis-inducing factor, is a sweat

gland AMP.[67] Dermcidin is reported to be decreased in atopic dermatitis and may contribute to altered bacterial carriage.[68] While there was no difference in dermcidin or dermcidin-derived peptides in sweat from HS patients compared to healthy volunteers, it has not been fully measured *in situ*.[34] Neither of these proteins have been specifically evaluated in apocrine glands in HS and a deficiency could lead to abnormal epidermal differentiation, primary follicular obstruction, and altered cutaneous microbiome activity.

Altered follicular infundibular anatomy and function

The infundibulum of the upper hair follicle has recently become an area of increased interest in HS because this is where the apocrine gland acrosyringium enters the hair follicle opening.[69] Expression of murine hair follicle infundibular proteins and transcription factors such as K79, LRIG1, and DLX have not been fully evaluated in healthy human apocrine glands or HS.[70-72] A PAS-negative zone has also been observed at the pilosebaceous junction.[73] Keratin 16, a marker of epidermal hyperproliferation, was increased in the infundibular epidermis of lesional HS skin.[74] As discussed above, inflamed HS follicular keratinocytes produced abundant pro-inflammatory mediators.[38] Overall, primary structural and functional changes at the infundibulum suggest possible mechanisms which may lead to subclinical follicular obstruction, poral occlusion, and infundibulitis.

Role of the cutaneous immune system

Activation of the cutaneous innate immune system is apparent in HS. This could be mediated by a dermal HS microbiome derived from the apocrine secretion-filled cyst. *Staphylococcal* and *Corynebacterium* species produce lipoproteins that activate TLR2 receptors,[75] which are increased on HS lesional antigen-presenting cells. Antigen presenting cells respond to TLR2 activation by releasing pro-inflammatory cytokines such as TNF and IL-12/23, which activate Th17 cells and keratinocytes. The innate immune system interprets the bacterial presence as a "foreign" organism that needs to be removed and mounts an exuberant reaction. There is also NLRP3 inflammasome activation, possibly by ectopic dermal keratin,[12] contributing to innate immune activation in the skin.

The role of keratinocytes in HS is not yet well defined. Aberrant follicular keratinocyte responses to bacteria, mechanical stress, or environmental triggers, have been suggested to predispose to inappropriate activation of the cutaneous innate immune system.[12,76] It has also been proposed that the early abnormality is in the terminal follicular epithelium, and that "dissecting terminal hair folliculitis" would be a more appropriate name for HS.[77] However, whether these keratinocyte responses are primary or secondary events remains to be determined. Furthermore, these keratinocyte reactions may not be specific to HS, as the cells and products found in HS lesions are consistent with immune amplification required for active effector immunity in the skin.[78]

The question also remains of how HS progresses from individual erythematous nodules to persistent suppurative tunnels in whole anatomical regions. The unrestrained chronic inflammation in HS may be a result of the inability to turn off the inflammatory response. Factors that may be responsible for this include the persistence of dermal biofilms in epithelialized tunnels and the presence of exhausted monocytes that are unable to fully respond to the inflammatory insult. There is also a relative increase of lesional and circulating Th17 cells (T regulatory cells have not yet been studied in HS), and possibly loss of negative regulators.[79] These factors favor ongoing and excessive activation of the cutaneous immune system and result in a failure to restore homeostasis.

Persistent cutaneous inflammation appears to lead to recruitment of the systemic immune system, and could also contribute to disease progression. The observations of systemic comorbidities and disease associations (Figure 1) suggest a systemic autoimmune disease. Other chronic diseases, such as psoriasis and rheumatoid arthritis share these systemic comorbidities, indicating possible common inflammatory pathways.[80] Ongoing studies across these different diseases will determine the primary pathogenic events shaping organ-related disease presentation and shared mechanisms of systemic inflammation.

Many chronic inflammatory diseases can be characterized using a molecular taxonomy of inflammatory cytokines.[81] For example, psoriasis can be classified as a disease of the IL-17/23 axis, atopic dermatitis as an IL-4/IL-13 disease, rheumatoid arthritis as an IL-6 disease, and juvenile inflammatory arthritis as an IL-1 mediated-disease.[81,82] While many of these diseases partially respond to TNF inhibition, there is an additional hierarchical structure of cytokine effects. Identification of the responsible cytokine in HS should lead to even more efficacious treatments.

One cytokine that may be playing an important role in the pathogenesis of HS is IL-6. A review of the effects of increased IL-6[83] reveals many symptoms that are seen in HS. The downstream effects of IL-6 include increased acute phase proteins, immunoglobulins, fever, neutrophilia, and anemia. IL-6 also causes an imbalance in the Th17 to Treg ratio, and increased IL-10. IL-6 stimulation may result in a reduction in albumin, transferrin, and zinc as well. It can cause pain, depression, and inflammatory arthritis, which are often seen in HS. There are many potential stimuli and sources of IL-6 in HS including macrophages, adipocytes, and stress responses. While it is premature to assume that increased IL-6 is responsible for the systemic effects of HS, it is a novel pathogenic hypothesis worthy of further exploration. If supported, there are anti-IL-6 treatments available that could be considered for HS in the future.[84]

Conclusion

As we are in the early stages of defining the pathophysiology of HS using modern molecular approaches, this review has focused on clinical observations and studies on lesional skin and the immune system to synthesize what they reveal about the causes of HS. It is clear that HS is a complicated disease, which results in great morbidity and impairment of quality of life. We do not yet have a complete understanding of the pathophysiology, and it is essential that we address this unmet need urgently. As we go forward, we can leverage our knowledge about other chronic immune-mediated diseases to guide future studies to help our suffering patients.

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