Hidradenitis suppurativa is an autoinflammatory keratinization disease: A review of the clinical, histologic, and molecular evidence

John W. Frew, MBBS, MMed, MSc
New York, New York

The pathogenic model of hidradenitis suppurativa is in the midst of a paradigm shift away from a disorder of primary follicular occlusion to an autoinflammatory keratinization disease. Observational, experimental, and therapeutic evidence supports the concept of hidradenitis suppurativa as a primarily inflammatory disorder, a disorder of autoimmunity, or both, in contrast to the current prevailing paradigm of primary follicular occlusion. The lack of reliable and high-fidelity disease models has limited the available experimental and mechanistic evidence to support or refute one pathogenic model over another. This scholarly review synthesizes the existing clinical, histologic, and molecular data to evaluate the extant evidence supporting the autoinflammatory paradigm and further informing the molecular mechanisms of hidradenitis suppurativa pathogenesis. Follicular hyperkeratosis/occlusion and perifollicular inflammation coexist in histologic specimens, with interleukin 1α demonstrated to stimulate comedogenesis in the infundibulum. pH elevation in occluded body sites alters the microbiome and amplifies existing T-helper cell type 17 immunoresponses. Known metabolic comorbidities and smoking are known to upregulate interleukin 1α in follicular keratinocytes. Identified genetic variants may alter epidermal growth factor receptor signaling, leading to upregulated keratinocyte inflammatory responses. The process of follicular rupture and dermal tunnel formation can be explained as secondary responses to inflammatory activation of fibroblasts and epithelial-mesenchymal transition, with antibody production associated with inflammatory amplification in advanced disease. This review aims to reevaluate and integrate the current clinical, histologic, and molecular data into a pathogenic model of hidradenitis suppurativa. This is essential to advance our understanding of the disease and identify novel therapeutic targets and approaches. (JAAD Int 2020;1:62-72.)

Key words: acne inversa; autoinflammatory; hidradenitis suppurativa; inflammation; mechanism; pathogenesis.
AND EXPERIMENTALLY A PRODUCT OF INFLAMMATION RATHER THAN A CAUSE

Follicular hyperkeratosis and comedogenesis coexist with perifollicular inflammation in hidradenitis suppurativa.1,4 Comedones are present in flexural and nonflexural inflamed and scarred tissues, as well as noninflamed tissues.9-11 Subclinical inflammation (observed in hidradenitis suppurativa)12,13 precedes comedogenesis in acne-prone skin.14-20 involving keratinocyte-derived proinflammatory mediators (lipoteichoic acid, CCL20, and interleukin [IL] 1α).18-24 Ex vivo studies of the follicular infundibulum25 isolated in vitro are able to recapitulate the formation of comedones with addition of IL-1α and prevent formation with the addition of IL-1 receptor antagonist.25 It is acknowledged that the in vitro studies performed are based on highly sebaceous follicular units that have distinct differences from apocrine-bearing skin26; however, the similarities in immunologic milieu between sebaceous and apocrine skin in T-helper cell 17—associated mediators27 (central to inflammation in hidradenitis suppurativa)28 raises the possibility that these mechanisms are shared. Molecular and ex vivo evidence suggests comedo formation may be secondary to subclinical inflammation. These results may explain the diffuse scattering of comedones observed in hidradenitis suppurativa—prone areas, the presence of comedones in extraflexural sites, and their presence in previously inflamed (“burned-out”) tissue or sites distant from a follicular unit.3,10

SKIN FOLD OCCLUSION IS ASSOCIATED WITH MICROBIOME ALTERATIONS AND SUBSEQUENT PROINFLAMMATORY KERATINOCYTE RESPONSES

From a clinical perspective, follicular occlusion may refer to anatomic sites of disease predilection (axillary, inguinal, and submammary folds).2 These areas demonstrate alterations in moisture, pH, and microbiological colonization6 (Fig 2), particularly in the setting of obesity.27-28 The follicular infundibulum is an immunologically active, microbiobally colonized site13,20 involved in the development of immune tolerance to commensal organisms.25-30 This differs substantially from other portions of the follicle (such as the bulb), which are considered immunologically privileged sites.32 Infundibular keratinocytes produce CCL20 and antimicrobial peptides under normal physiologic conditions25 (Fig 2). Increasing moisture decreases the pH of the stratum corneum,26,29 promoting the colonization and activity of hidradenitis suppurativa—associated microorganisms (eg, Porphyromonas33,34 (Fig 2)). Other bacteria,35-36 yeasts,37 and associated proteins (including lipoteichoic acid) induce the release of preformed IL-1α in keratinocytes.38 Indirect evidence for the role of yeasts in inflammatory activity in hidradenitis suppurativa39 has been demonstrated in recent observational studies.39,40

Although the precise mechanisms of specific microbiological species and strains in hidradenitis suppurativa is ill defined, their functional role in producing an aberrant proinflammatory response (either directly or indirectly via keratinocytes) is consistent with observational studies identifying these microbionts in both early and advanced disease.34,35

CAPSULE SUMMARY

- Hidradenitis suppurativa is known as a disorder of follicular occlusion, with inflammation being a primary manifestation of disease. Clinical, histologic, and molecular evidence suggests that inflammation is central to multiple aspects of disease, but this remains poorly integrated into the existing pathogenic paradigm.

- Histologic and molecular evidence supports the concept of inflammation as the primary driver of disease activity in hidradenitis suppurativa. It enables explanation of observed events such as follicular rupture, tunnel formation, and systemic inflammation, which are poorly described in the follicular occlusion paradigm. Hidradenitis suppurativa is an autoimmune keratinization disease. Reframing our pathologic and clinical understanding in the context of this paradigm is vital to identify and implement novel therapeutic strategies for this burdensome disease.

INFLAMMATION IN HIDRADENITIS SUPPURATIVA: EVIDENCE FROM EXISTING STUDIES

The inflammatory signature of established hidradenitis suppurativa has been well characterized in multiple histologic26,41 and molecular studies.26,42-45 Similarities and parallels with psoriasis26 have been observed in lesional and perilesional hidradenitis suppurativa tissue,26,46 with lesional nodules demonstrating mixed inflammatory infiltrates comprising T cells, dendritic cells, plasma cells, neutrophils,17-50 and monocytes.51 Chronic long-
**Abbreviations used:**

EGFR: Epidermal growth factor receptor  
IL: Interleukin

Standing disease appears auto-inflammatory, and also demonstrates B-cell infiltrates, and development of epithelialized tunnels. An issue with understanding the characteristics of inflammation in hidradenitis suppurativa is that the majority of specimens isolated for studies are from individuals with severe, long-standing disease. Given that hidradenitis suppurativa is morphologically diverse, it would be erroneous to assume that a biopsy from one portion of tissue is representative of all the different epidermal (and deep dermal) morphologies present across the spectrum of hidradenitis suppurativa. Therefore, studies that do not define the severity, treatments, sites, and lesion types of biopsies should be interpreted with caution.

The mechanisms of lesion development are unclear because perilesional inflammation is of the same character (albeit less intense) as nearby lesional inflammation; however, lesional cytokine profiles are unable to be experimentally generated from the addition of IL-1α, IL-1β, or both to perilesional tissue. This raises the prospect that the process of inflammation in hidradenitis suppurativa is more complex than initially thought and that the inflammatory characteristics of perilesional tissue are distinct from those of lesional tissue.

**Disease Initiation Is Associated With Systemic Subclinical Inflammation and Dysregulated Infundibular Keratinocytes**

Understanding of the initiating factors associated with the excessive and self-perpetuating perifollicular inflammation in hidradenitis suppurativa remains incomplete. Epidemiologic and clinical observations suggest that a number of systemic disorders (including insulin resistance, hormonal dysregulation, and obesity) may be associated with hidradenitis suppurativa and contribute to a proinflammatory state. Adipose tissue can produce proinflammatory signatures, including IL-6, IL-1β, and tumor necrosis factor-α in the setting of chronic nutrient excess. Additionally, adipokines can mediate both inflammation and the development of insulin resistance (Fig 2), which is also associated with hidradenitis suppurativa. Keratinocytes in the infra-infundibulum of the follicle express type 1 5-hydroxytestosterone, modulating infundibular keratinocyte differentiation programs both directly and via fibroblast activation and fibroblast-keratinocyte interactions, contributing to androgen-induced follicular changes.

Overall, these associations suggest that a systemic proinflammatory state and localized infundibular keratinocyte dysregulation are potential predisposing factors to clinical disease. There are contradictory reports pertaining to the benefit of withdrawing these predisposing factors (eg, cessation of smoking, weight loss) during established disease. These findings appear contradictory only if one holds the assumption that the initiating and perpetuating factors of clinical disease in hidradenitis suppurativa are one and the same. As other authors have suggested, there may be unique factors contributing to each state (initiation of disease and perpetuation of disease); and our lack of data regarding early (subclinical) disease has not allowed us to appreciate this fact.

**T-Helper Cell 17 Feed-Forward Inflammation Is Prominent in Established Disease**

The T-helper cell 17 axis is strongly implicated in established self-perpetuating clinical disease; however, the mechanisms leading to T-helper cell 17 feed-forward self-amplification in hidradenitis suppurativa are still unclear. It is assumed to be similar to the activation of the T-helper cell 17 axis in psoriasis, with the predisposition of the axillae and other areas of apocrine-gland-rich skin to a T-helper cell 17 immunoresponsiveness, as demonstrated...
There is well-documented evidence (largely from the psoriasis literature) regarding feed-forward mechanisms between IL-1β, IL-6, and tumor necrosis factor-α by IL-17, leading to further IL-1β, IL-6, and tumor necrosis factor-α production, as well as downstream activation of acute phase reactants and neutrophilic and complement-mediated inflammatory responses. This is further perpetuated through leucocyte-keratinocyte interactions, further amplifying antimicrobial peptide and chemokine production (including CXCL1 and CXCL8), leading to further inflammatory cell recruitment adjacent to IL-17-activated epidermal keratinocytes (Fig 3). Such inflammatory cell localization has been observed surrounding intrafollicular and interfolicular sites adjacent to epidermal keratinocytes in early histologic specimens of hidradenitis suppurativa, with evidence of early psoriasiform hyperplasia suggestive of IL-17-induced epidermal changes. Despite that the majority of translational work focuses on IL-17A (given the body of preexisting experimental evidence).
work based on psoriasis), significant elevations of other IL-17 isoforms, including IL-17C and IL-17F, are observed in hidradenitis suppurativa tissue, and these may be significant contributors to disease activity that are not targeted by anti-IL-17A therapies alone.

THE ROLE OF B CELLS, DESPITE THEIR DOMINANCE, REMAINS UNCLEAR

Long-standing and severe disease may have a unique inflammatory profile compared with milder or less established forms of hidradenitis suppurativa. Histologic and transcriptomic studies have identified a high level of B-cell and plasma-cell signatures, complement (specifically C5a) activation, and extensive tissue remodeling via matrix metalloproteinases with subsequent destruction of follicular and glandular structures in the dermis.

The role and characteristics of B cells in mild to moderate hidradenitis suppurativa are unclear. The presence of B cells and plasma cells in skin and blood suggests the possibility that some component of severe or long-standing hidradenitis suppurativa may be an autoimmune or antibody-mediated disorder. However, to date no product has been definitively identified as an autoimmune target for the disease. B cells are present in other chronic inflammatory disorders without known

Fig 2. Initiating factors in hidradenitis suppurativa. Normal control skin (first panel from the left) from hidradenitis suppurativa–associated cutaneous sites (eg, axilla) have normal colonizing microbionts (including within the follicular infundibulum), which are continuously monitored by circulating immune cells in homeostasis (circulating to and from regional lymph nodes (inset in first panel from the left). Known predisposing factors, including skin occlusion (second panel from left), predisposing genetic mutations (third panel from the left), and proinflammatory comorbidities such as obesity and insulin resistance, increase the inflammatory drive of infundibular keratinocytes (purple rectangular cells) via varied mechanisms. Skin occlusion (second panel from the left) alters the microbiological composition of the skin (red and yellow microbionts) via increases in cutaneous pH. These microbionts increase the production of CCL20 and interleukin (IL) 1α by infundibular keratinocytes. Genetic mutations in the γ-secretase complex are known to affect Notch signaling and also substrates including epidermal growth factor receptors, which are active in the follicular infundibulum. Dysregulation of EGFR signaling is known to increase CCL20 and IL-1α production by infundibular keratinocytes. Metabolic comorbidities produce increased levels of circulating tumor necrosis factor-α, IL-1β, and IL-6. These mediators stimulate CCL20 and IL-1α production.
autoimmune targets, including psoriasis and atopic dermatitis. In these conditions, they are thought to be bystanders (secondary to combined B-cell and T-cell chemoattractants such as CXCL13 or CCL20) or secondary amplifiers of T-cell–mediated inflammation. (Fig 3). Byrd et al demonstrated that antibodies to citrullinated peptides contribute to the development of neutrophil extracellular traps in advanced disease, with parallels to B-cell and neutrophil extracellular traps in rheumatoid arthritis. Case reports of rituximab ameliorating hidradenitis suppurativa disease activity are known, but overall, the role of B cells as bystanders, amplifiers of existing inflammation, or central pathogenic players is unclear and requires further investigation.

Fig 3. Mechanisms of tunnel formation, follicular rupture, and perpetuation of inflammation in hidradenitis suppurativa. Development of tunnels (top panel): Inflammation adjacent to the follicular outer root sheath activates fibroblasts, with stromal-keratinocyte feedback resulting in keratinocyte outgrowth from the follicular wall. The ongoing keratinocyte outgrowth results in keratinocyte-mediated inflammatory cell recruitment, further amplifying the stromally mediated keratinocyte outgrowth in a positive-feedback loop. The inflammatory cells are attracted to the keratinocyte chemokine (CXCL1/CXCL8) gradient, resulting in migration into the lumen of the tunnels. Mechanisms of follicular rupture (middle panel): The inflammatory infiltrate is associated with high levels of matrix metalloproteinases, which degrade the reticular lamina. Keratinocyte-leucocyte cross talk activated epithelial-mesenchyme-transition mechanisms, leading to degradation of the basement membrane zone, loss of hemidesmosomes and desmosomes, and keratinocytes expressing mesenchymal cell surface markers (yellow keratinocytes). Eventually, the follicular wall is disassembled, replaced by mesenchymal cells and dense inflammatory infiltrates. Mechanisms of inflammatory amplification (bottom panel): Activated keratinocytes interact with inflammatory and stromal cells via various pathways to result in activated fibroblasts, T-helper cell types 1 and 17, and infiltration of dendritic cells and neutrophils. Circulating B cells (circulating to and from regional lymph nodes; far right of lower panel), activated by the high-interferon-mediated milieu, interact with multiple cell types to amplify existing inflammatory loops, as well as recirculate in the lymphatic and vascular system, contributing to systemic inflammation.

D, Desmosome; HD, hemidesmosome; MMP, matrix metalloproteinase; ORS, outer root sheath.
GENETIC VARIANTS IN HIDRADENITIS SUPPURATIVA MAY ACT VIA EGFR-ASSOCIATED PATHWAYS LINKING FOLLICLES, T-HELPER CELL 17–MEDIATED INFLAMMATION, AND DRUG-INDUCED DISEASE

A minority of patients with familial and spontaneous hidradenitis suppurativa have been identified with GSC mutations. The precise mechanism of action of GSC mutations in the pathogenesis of hidradenitis suppurativa is unclear. The GSC complex cleaves more than 70 different substrates involved in cell cycle and inflammation, including epidermal growth factor receptor (EGFR), IL-1, tumor necrosis factor-α, and Notch. Notch is proposed as the unifying motif in hidradenitis suppurativa pathogenesis via associations with keratinocyte proliferation, smoking, and sequence variants in GSC. However, Notch dysregulation is also present in multiple other inflammatory dermatoses, arguing against a unique role in hidradenitis suppurativa. In silico evidence has identified ERbb4 and Tie1 as differentially expressed GSC substrates that distinguish the transcriptome of hidradenitis suppurativa from familial Alzheimer disease and other inflammatory skin diseases. These components of the EGFR pathway (active in the follicular infundibulum) are associated with SOX9 and Wnt signaling linked with hair cycle progression, IL-17A production (through shared downstream Act1 activity), and epithelial cell fate. All mechanisms identified in transcriptomic analysis of hidradenitis suppurativa tissues, GSC knock-down results in IL-36α production, alterations in EGFR signaling, and increased sensitivity to interferon-mediated proinflammatory pathways (Fig 2). POFUT-1 (identified in cases of Dowling-Degos disease associated with hidradenitis suppurativa) is a fucosyltransferase that is active on multiple substrates, including Notch and EGFR, and is important for posttranslational modification of receptors. This suggests a role for EGFR signaling in hidradenitis suppurativa, supported by reports of hidradenitis suppurativa associated with use of EGFR antagonists in oncology.

THE EVIDENCE AND PROPOSED MECHANISMS FOR FOLLICULAR RUPTURE

Follicular rupture is proposed as the primary mechanism by which follicular occlusion leads to dermal inflammation in hidradenitis suppurativa, but the molecular mechanisms remain unclear. Observational studies demonstrate the coexistence of dense perifollicular and intrafollicular inflammation and discontinuities in follicular epithelium in affected tissues (Fig 3). Long-standing disease demonstrates a noticeable absence of follicular and adnexal structures, consistent with profound dermal inflammation. A reduction in the thickness of the fibroreticular lamina surrounding follicles and sebaceous glands has been observed. Occluded follicles in other conditions (such as epidermal inclusion cysts) are testament to the potential size intrafollicular collections may progress to before rupture. However, the early presence of inflammation in hidradenitis suppurativa lesions suggests an inflammation-related mechanism that is well documented to disassemble the basement membrane zone as part of the wound-healing process. Epithelial-mesenchymal transition pathways are part of the normal wound-healing response and have been identified in transcriptomic analysis of hidradenitis suppurativa tissues. It may also explain the presence of keratin-staining cells in the dermis of hidradenitis suppurativa sections (via keratinocytes undergoing epithelial-mesenchymal transition but still expressing keratin proteins), the destruction of follicular and adnexal structures in advanced disease, and the development of dermal tunnels (Fig 3). Similar inductions in epithelial-mesenchymal transition-associated signaling pathways are observed in malignancy and wound healing and contribute to the metastatic potential of cancer and long-standing wounds. Hence, the concept of follicular rupture may be more appropriately described as a process of “follicular disassembly” induced by the chronic inflammatory changes via epithelial-mesenchymal transition and aberrant extracellular remodeling wound-healing programs.

DERMAL TUNNELS ARE ACTIVE INFLAMMATORY STRUCTURES AND THEIR DEVELOPMENT IS ORCHESTRATED BY DERMAL INFLAMMATION

Dermal tunnels in hidradenitis suppurativa are unique structures comprising stratified squamous epithelia that recapitulate the structure of the overlying epidermis and produce active inflammatory mediators. This is in contrast to other tunnel-like structures in chronic inflammatory conditions such as fistulizing Crohn’s disease, which do not recapitulate mucosal structures with the same degree of fidelity. The mechanisms leading to tunnel formation are unclear; however, it is hypothesized that these tunnels derive from the aberrant keratinocyte outgrowth from the outer root sheath of the
CONCLUSIONS

The available histologic and molecular evidence suggests inflammation is a central component to the pathogenesis of hidradenitis suppurativa. Placing inflammation as the primary driver of disease provides a scaffold for testable hypotheses regarding polygenic risk loci for the development of hidradenitis suppurativa, drug-induced causes of hidradenitis suppurativa, the development of dermal tunnels, and the inflammatory proliferative gelatinous mass, which are currently poorly integrated into the follicular occlusion model of hidradenitis suppurativa (Fig 1). More mechanistic and translational investigations are needed to further evaluate the role of genetics and B cells in hidradenitis suppurativa, as well as provide mechanistic evidence about the development of follicular rupture and tunnel formation. Such basic cellular and molecular investigations are vital to develop our understanding of the disease. Realigning the pathogenic paradigm with the molecular evidence is essential to enable the identification and exploration of novel targets, interventions, and therapeutics for this chronic debilitating disease.

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Tunnels do not extend into the subcutaneous tissues or fistulize with other hollow organs (except in the context of coexistent inflammatory bowel disease), suggesting an association with signaling from the dermis. This parallels the development of the hair follicle and early anagen downgrowth in the hair cycle, which are mediated via platelet derived growth factor α-derived signaling from the dermal condensate. Platelet derived growth factor α-mediated signaling has also been identified in transcriptomic data from hidradenitis suppurativa—associated fibroblasts. Given that these fibroblast-derived signals are secondary to inflammation-mediated epigenetic modifications, it is plausible to assume that the development of tunnels is an inflammation-driven process. However, once these tunnels are established, the CXCL1/8 gradient established across the epithelia (including tunnels) results in transepithelial neutrophil trafficking and neutrophil extracellular trap formation in tunnel lumen. This results in development of the infiltrative proliferative gelatinous mass and biofilm formation in hidradenitis suppurativa tunnels. This in turn drives further inflammatory recruitment surrounding these established tunnels, leading to the ongoing cycle of severe intractable inflammation and drainage.
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