The pathogenesis of hidradenitis suppurativa: Evolving paradigms in a complex disease

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Abstract
Hidradenitis suppurativa is a complex inflammatory skin disease with the molecular pathogenesis of disease incompletely understood. Recent observational and experimental insights into disease pathogenesis are challenging long-held beliefs regarding the causes and mechanisms of disease. The most effective treatments to date are anti-inflammatory in nature suggesting inflammation is the major driver of disease activity. This study critically evaluates the existing literature regarding the mechanisms of disease pathogenesis. Specifically, it questions the role of follicular occlusion as the central driver of disease activity and reframes hidradenitis suppurativa as a complex autoinflammatory and autoimmune disorder. Ongoing efforts to understand the mechanisms of disease will no doubt lead to more efficacious therapeutics to control this burdensome disabling disease.

KEYWORDS
acne inversa, cause, hidradenitis suppurativa, inflammation, pathogenesis

1 | INTRODUCTION

Hidradenitis suppurativa (HS) is a complex inflammatory disorder manifesting in chronic, recurrent, painful nodules abscesses, and malodorous draining tunnels with a predilection for flexural areas of skin. The disease has features of both autoinflammation and autoimmunity with a variety of inflammatory pathways and cell types involved. The precise pathogenesis of the disease is incompletely understood. Historically, HS has been considered a disorder of follicular occlusion, however, novel insights have suggested it may come under the spectrum of an autoinflammatory keratinization disease (AiKD). Limitations to our understanding of the pathogenesis of HS include the lack of a reliable animal model of disease and the identification of significant inflammatory heterogeneity.

Continual re-evaluation and integration of current clinical, histological and molecular data into our pathogenic model of HS is essential to advance our understanding of the disease. Challenging existing paradigms through observation, hypothesis, and experimentation (and separating the interpretation of these results from personal self-interest) is a core component of the scientific process; and is essential to enable accurate identification of novel therapeutic targets and treatment strategies. It is also vital to the understanding of differential treatment response in different individuals and exploring the potential role of variations in inflammatory endotypes in the disease; in a similar way to how this has been identified in atopic dermatitis. This review aims to synthesize existing knowledge from clinical observation, classical histology, as well as modern molecular biology techniques to evaluate the evidence for HS as either a disorder of follicular occlusion or an AiKD.
Historically, HS has been proposed to be a disorder to apocrine gland inflammation, although multiple independent histological studies have demonstrated that inflammatory involvement of apocrine glands is a secondary phenomenon, and that the primary inflammatory drive of the disease exists adjacent to keratinocytes of the follicular infundibulum and interfollicular epidermis. It is now widely accepted that the primary drive of disease activity centers upon the follicular infundibulum (Figure 1). Additionally, other disorders such as pilonidal sinus disease and dissecting cellulitis of the scalp share many clinical, histological, and inflammatory features with HS and are beginning to be considered as uni-localized variants of disease. Melnik’s seminal 2013 paper began to shift the pathogenic paradigm of HS away from an apocrine-gland-based inflammatory or infectious disorder, to a disorder of follicular occlusion and proposed dysregulated Notch signaling as the unifying feature of HS pathogenesis.

Emerging evidence as to the role of the inflammasome, complement, and IL-1 isoforms has led to the suggestion of HS as an AiKD. Evidence of systemic inflammation, activation of complement, and IL-1 isoforms has led to the suggestion of HS as an AiKD. Evidence of systemic inflammation, activation of complement, and IL-1 isoforms has led to the suggestion of HS as an AiKD.
B cells and plasma cells have raised the possibility of HS having an autoimmune or antibody-mediated component. However, follicular occlusion is still considered the "primem mover" of HS preceding the inflammatory drive of disease.

3 | FOLLICULAR OCCLUSION

3.1 | Comedones are clinically and experimentally a product of inflammation, rather than a cause

Histological studies illustrate the prominent role of comedogenesis, follicular hyperkeratosis, and comedogenesis in HS tissue. However, in each instance, the coexistence of perifollicular inflammation is comparably prominent. Clinically, comedones (both open and closed) as well as typical double-sided comedones are present in diseased areas, inflamed tissues, and also in scarred, noninflamed tissues. They are also present in areas not exposed to flexural occlusion.

Von Laffert et al. report comedones as more common in end-stage fibrotic and scarred lesions and independent of the follicular unit. These comedones are more likely to be those of the double-ended variety which were once pathognomonic of HS. From these clinical observations, we can conclude that comedones are associated with HS, however, the establishment of causation requires mechanistic evidence. Such mechanistic evidence is available thanks to Investigations into comedogenesis in acne research. Recent findings have identified subclinical inflammation as preceding comedogenesis in acne prone skin disrupting the long-standing assumption that follicular occlusion is the primary initiating factor in acne. The molecular mechanisms of comedogenesis involve follicular keratinocytes producing a number of pro-inflammatory mediators (including antimicrobial peptides, microbial associated proteins including Lipotechoic acid, CCL20, and IL-1α). Ex vivo studies of the follicular infundibulum isolated in vitro are able to recapitulate the formation of comedones with addition of IL-1α and prevent formation with the addition of IL-1RA. While these studies were focused upon highly sebaceous follicular units which are distinctly different from skin-bearing apocrine glands, the Th17 associated mediators which are involved in the HS inflammatory response are similar. Therefore, these in vitro studies highlight the theoretical prospect of these immunological mechanisms being common between different anatomical locations. Reproduction of these experiments using follicular infundibular from apocrine gland bearing regions would hopefully be definitive in confirming or refuting these findings. Ongoing clinical trials using IL-1α antagonists (such as Bermekimab) may contribute to our knowledge in this area.

Therefore, we can conclude that molecular and ex-vivo evidence suggests comedone formation is possible secondary to subclinical inflammation, rather than inflammation solely being the result of comedone formation and follicular rupture. The precise mechanisms have been demonstrated in human skin, however, require validation in apocrine gland bearing skin given the unique immunological milieu of these sites. These results may explain the diffuse scattering of comedones seen in HS prone areas, the presence of comedones in extra-flexural sites and the presence of comedones in previously inflamed ("burnt out") tissue or sites distant from a follicular unit. It also raises the additional question of what differentiates conditions in which subclinical inflammation and diffuse flexural comedone formation (such as Dowling-Degos disease) exist, from highly inflammatory HS lesions. Direct molecular comparisons of these conditions may further inform the differences in subclinical inflammation that leads to the development of one condition over another (or indeed the coexistence of both conditions at different timepoints).

3.2 | Skin fold occlusion is associated with microbiome alterations and subsequent pro-inflammatory keratinocyte responses

On a microscopic level, follicular occlusion in HS refers to occlusion of the follicle at the infundibulum, however, clinically, "follicular occlusion" tends to be associated with specific body sites including the axillae, inguinal flexures, and sub-mammary folds. These are areas of predilection in HS as they prone to increased frictional trauma, altered pH, increased moisture levels, and microbiological colonization.

Among obese patients, the posterior neck folds, abdominal pannus, gluteal cleft, and inner thighs, and other anatomical sites can undergo similar microbiological milieu alterations secondary to heat, moisture, and pH changes.

The follicular infundibulum is significantly different to other parts of the hair follicle (including the bulb) because of its immunologically active nature and its related role in developing an immune tolerance to commensal micro-organisms. Healthy infundibular keratinocytes functioning within a normal physiological environment are responsible for producing CCL20 as well as antimicrobial peptides. Due to the increased moisture and reduced pH of the stratum corneum that HS causes, colonization of porphyromonas species. Further, the release of pre-formed 1α in keratinocytes can be provoked by bacterial specials other than porphyromonas (including Staph Aureus and Propionibacterium ances) (Figure 1). Additionally, there is ancillary evidence suggesting that yeasts play a role in the inflammatory process of HS.

Recent observational research has demonstrated that anti-saccharomyces cerevisiae antibodies (present in severe HS disease) can cross react with other fungi and bacteria. The specific mechanism of such microbiological specials remain poorly understood, however, their significant role in producing a pro-inflammatory response (via keratinocytes either directly or indirectly) has been demonstrated in observational studies investigating both early and advanced HS.

4 | INFLAMMATION

4.1 | Inflammation in HS: evidence from existing studies

Histopathological examination of HS lesional tissue demonstrates mixed inflammatory infiltrates including T cells, plasma cells,
neutrophils, dendritic cells, and monocytes. Further, patients who have long-standing disease show additional histopathological findings including B cell infiltrates, NETosis, and epithelialized tunnels. HS has been shown to be an inflammatory disease in multiple molecular and histological studies. Despite this principle being well established, it must be recognized that the majority of biological samples (HS lesional tissue) was taken from patients who have longstanding and severe disease. Additionally, until very recently, standardized biopsy sites and requirements had not been defined for HS tissue studies. These factors have lead to two limitations in our current understanding of HS as an inflammatory process. First, there is a lack of studies investigating early HS disease and factors which may precede or provoke HS development. Second, because HS has multiple morphologies, it cannot reliably be concluded that a biopsy taken from one site is representative of the various morphologies that exist within the spectrum of HS disease. For these reasons, it is important to review and consider any study results which do not specify such factors (disease severity and the anatomical location of tissue samples) with caution.

The common inflammatory signatures on qRT-PCR identified in HS studies of lesional tissue include TNF-α, IL-1α, IL-1β, IL-6, IL-17A, IL-17F, IL-32, IL-36α, IL-36g, and IL-10. Additional chemokines include CCL3, CCL5, CCL27, and BLC. Nonlesional tissue also demonstrates upregulated levels of many of these cytokines although variation does exist due to previous lack of standardized biopsy sites and combination of both partially treated as well as untreated specimens. RNAseq transcriptomic studies demonstrate strong B-cell signatures with IgG1 and IgG3 immunoglobulins and aspects of the complement cascade highly upregulated. Additionally, signals of keratinocyte hyperplasia (Keratin 6, Keratin 16) are also seen with keratinocyte derived factors being elevated in lesional and perilesional tissue compared with unaffected and control skin. Variation in cytokine levels do occur (between lesional, peri-lesional, and nonlesional tissue) in terms of type and degree of inflammation although reliable characterization of inflammation matched with disease morphology (e.g., nodules vs. tunnels) is yet to be undertaken. Scarred tissue demonstrates decreased inflammatory profiles compared to nonscared areas and the presence of occult dermal tunnels can also induce highly inflammatory profiles in normal-appearing skin. The use of clinical ultrasound has been suggested as a method of confirming or excluding the presence of tunnels before biopsy.

Analysis of serum has identified IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α as upregulated in multiple studies, however, conflicting results exist between studies between serum levels of IL-10, IL-17, and IFN-γ which may be secondary to the severity of included participants and the methods of cytokine analysis. The majority of data regarding serum inflammation is based upon patients with Hurley stages 2 and 3 disease with the changes in serum inflammatory markers in early and mild disease unclear.

In terms of establishing mechanism—it has been assumed (based on observational studies) that perilesional inflammation is of the same character (albeit less intense) than nearby lesional inflammation. Therefore, given the known feedback mechanisms between IL-1 and IL-17 leading to self-perpetuating feed-forward inflammation, it is reasonable to assume that lesional tissue inflammatory characteristics may be replicated by adding pro-inflammatory cytokines to perilesional tissue. This experiment (conducted by Vossen et al.) was unable to replicate the lesional HS inflammatory profile suggesting that IL-1α and/or IL-1β are not the sole triggers necessary to induce the development of lesions in HS. Other possibilities are that a combination of multiple inflammatory mediators are required; or as-yet-unknown predisposing factors are involved in inducing active inflammatory nodules on a background of perilesional subclinical inflammation. This raises the prospect that the process of inflammation in HS is more complex than initially thought. The underlying assumption thus far in HS research is that perilesional tissue represents the same inflammatory profile as lesional tissue, differing only in the degree, intensity, and more superficial location of inflammation. However, an alternative hypothesis, that the inflammatory characteristics of perilesional tissue is distinct from lesional tissue remains to be thoroughly investigated.

4.2 Disease initiation is associated with systemic subclinical inflammation and dysregulated infundibular keratinocytes

The site of initial inflammation in HS is centered upon the infundibulum of the hair follicle. Given the active immunologic role of the follicular infundibulum, a degree of baseline inflammatory activity around the follicle is considered normal. Our understanding, however, of the factors which initiate and perpetuate the moderate and self-perpetuating peri-follicular inflammation associated with the pathogenesis of HS is not complete. Multiple factors such as hormonal dysregulation, insulin resistance, and obesity have been suggested as possible associations of HS disease which may contribute to a generalized pro-inflammatory state. Furthermore, diseases such as psoriasis, rheumatoid arthritis, and atherosclerosis, which are all inflammatory disorders themselves, have also been associated with HS. While these associations have been made, the causative mechanisms between systemic inflammation and HS are unclear and require further investigation.

Despite the causative mechanisms between systemic inflammation and HS, clinical guidelines and limited clinical evidence indicate that there are benefits to reducing systemic inflammation via weight loss and smoking cessation. The mechanisms of these pro-inflammatory cascades are complex and incompletely understood. Smoking, via polycyclic aromatic hydrocarbons can directly alter follicular keratinocyte differentiation resulting in comedogenesis. It can also produce widespread methylation changes and systemic increases in IL-6, CRP, Fibrinogen, and multiple members of the NF-kB family. Adipose tissue can produce pro-inflammatory signatures including IL-6, IL-1β, TNF-α in the setting of chronic nutrient excess. Additionally, adipokines can mediate
both inflammation and the development of insulin resistance\(^9\) which is also associated with HS.\(^7\) Keratinocytes in the infra-infundibulum of the follicle express Type 1 and 5 hydroxy-testosterone\(^9\); modulating infundibular keratinocyte differentiation programs both directly as well as via fibroblast activation and fibroblast-keratinocyte interactions,\(^9\) contributing to androgen-induced follicular changes.\(^9\)

These associations indicate that systemic inflammation and infundibular keratinocyte dysregulation are likely to be factors which pre-dispose patients to suffer from clinical disease.

There are contradictory reports\(^9\) regarding the advantages of minimizing systemic inflammation via weight loss and smoking cessation once HS disease is established. These reports are contradictory only if it is assumed that the initiating disease factors and perpetuating disease factors are the same. Multiple authors,\(^9\) however, have suggested that there may be idiosyncratic factors which contribute separately to disease initiation and perpetuation. These authors suggest that the lack of research and available data investigating early or subclinical HS has not allowed the medical community to acknowledge this concept.\(^9\)

5 | TH17 FEED-FORWARD INFLAMMATION IS PROMINENT IN ESTABLISHED DISEASE

While the mechanisms behind Th17’s role as a feed-forward self-amplifier in HS remains uncertain, it is well established that the TH17 axis is strongly implicated with clinical disease.\(^9\) It has been presumed that the activation of the TH17 axis in HS is similar to that of it’s activation in psoriatic disease. A predisposition of a Th17 immune response at cutaneous locations that are apocrine gland rich (such as the axillary regions) has been experimentally indicated.\(^9\)

Literature regarding psoriatic disease presents well-established evidence surrounding the positive feedback loops (or “feed-forward mechanisms”) that exists between IL-1\(β\), IL-6, and TNF-\(α\) by IL-17 leading to further IL-1\(β\), IL-6, and TNF-\(α\) production as well as downstream activation of acute-phase reactants, neutrophilic and complement-mediated inflammatory responses.\(^9\) This is further perpetuated through leukocyte-keratinocyte interactions.\(^9\)\(^9\) further amplifying antimicrobial peptide and chemokine production (including CXCL1 and CXCL8)\(^9\) leading to further inflammatory cell recruitment adjacent to IL-17 activated epidermal keratinocytes. Such inflammatory cell localization has been seen surrounding intrafollicular and interfollicular sites adjacent to epidermal keratinocytes in early histological specimens of HS.\(^9\)\(^9\)\(^9\)\(^9\) with evidence of early psoriasiform hyperplasia suggestive of IL-17 induced epidermal changes. Despite the majority of translational work focusing upon IL-17A (given the body of pre-existing work based in psoriasis), significant elevations of other IL-17 isoforms including IL-17C and IL-17F are seen in HS tissue.\(^9\)\(^9\)\(^9\)\(^9\) and these may be significant contributors to disease activity which are not targeted by anti-IL-17A therapies alone. Ongoing clinical trials using IL-17 antagonists such as Secukinumab and Bimikizumab will help identify the clinical relevance of IL-17 blockade in HS.

5.1 | The role of B cells, despite their dominance, remains unclear

As previously suggested, the inflammatory profile of longstanding or severe HS may differ from the inflammatory profile of milder disease activity. Significant levels of B-cell and plasma signatures, complement activation, and tissue remodeling through matrix metalloproteinases causing demolition of dermal follicular and glandular structures have been demonstrated in both histological and transcriptomic research.\(^9\)\(^9\)\(^9\) The distinguishing features and the role that B cells play in mild to moderate HS disease remains unclear. The existence of plasma cells and B cells in both tissue and blood\(^9\)\(^9\) indicates that a longstanding and severe HS may secondary to autoimmune or antibody mediated dysregulation. No product or cell, however, has been identified as an autoimmune target among HS patients.\(^9\) In other dermatological inflammatory diseases such as eczema and psoriasis, B cells are also present but, similar to HS, no known autoimmune targets have been identified.\(^9\) Researchers have suggested that the B cells are secondary to combined B cell and T cell chemo-attractants (CXCL13 or CCL20) and thus amplify inflammation that is mediated by T cells.\(^9\) A study by Byrd et al.\(^9\) indicated that antibodies to citrullinated peptides contribute to the development of neutrophil extracellular traps (NETs) in advanced disease with parallels to B cell and NETs in Rheumatoid Arthritis.\(^9\) Further, there are some case reports which demonstrate rituximab leading to resolution of disease among HS patients,\(^9\) further supporting the idea of B cells play a role in amplifying existing inflammation. Recent mechanistic studies have identified B cells as the target of anti-TNF therapy in severe HS, with Adalimumab downregulating levels of B cells and plasma cells in HS lesional tissue.\(^9\)\(^9\)\(^9\) This suggests that the role of B cells is central in the efficacy or lack of efficacy of therapeutics in HS and is a much needed area of further research.

5.1.1 | Genetic variants in HS may act via EGFR-associated pathways linking follicles, Th17 mediated inflammation, and drug-induced disease

The role of inherited mutations in Notch signaling as the pathogenic mechanism in HS has come under scrutiny,\(^9\)\(^9\)\(^9\)\(^9\) with the existing genetic and molecular evidence suggesting a more complex interplay between genetics and infundibular keratinocyte-derived inflammation.

The first documented mutation in familial HS (in Nicastrin a component of the gamma secretase complex [GSC]) was identified in 2010 in an East-Asian kindred.\(^9\)\(^9\) Mutations in the GSC are also associated with familial Alzheimer’s disease\(^9\)\(^9\) and cardiomyopathy\(^9\) although no common variants with HS are known. Since then a small minority of patients with familial and spontaneous HS have been identified with GSC mutations.\(^9\) This suggests that other identified loci may contribute to genetic predisposition to HS, although this will be only be elucidated with the results of Genome Wide Association studies in HS. The exact mechanism of action of
GSC mutations in the pathogenesis of HS is unknown. What is known, however, is that over 70 substrates are involved in the cell cycle and inflammation (such as EGFR, IL-1, TNF-α, and Notch) are cleaved from the GSC complex. Melnik and Plewig proposed that Notch signaling is the unifying element in HS pathogenesis via associations with keratinocyte proliferation, smoking, and sequence variants in GSC. The molecular evidence for Notch being associated with keratinocyte hyperproliferation is well established, however, dysregulated Notch signaling is also associated with other inflammatory skin disorders including psoriasis, atopic dermatitis, and alopecia areata. Notch dysregulation may be an epiphenomenon secondary to keratinocyte proliferation (as it is present in multiple other inflammatory dermatoses) rather than the primary cause of HS.

In silico evidence has identified HS-specific GSC substrates ERbb4 and Tie1 as differentially expressed substrates that distinguish the transcriptome of HS from familial Alzheimer’s disease and other inflammatory skin diseases. ErbB4 and Tie1 are components of the EGFR pathway (active in the follicular infundibulum) and 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 HS tissues.

In vitro studies have demonstrated diverse pro-inflammatory results of Nicasin knockdown including IL-36a production, alterations in EGFR signaling as well as increased sensitivity to interferon mediated pro-inflammatory pathways. Recently, mutations in POFUT1 have been identified in cases of Dowling Degos Disease associated with HS. POFUT-1 is a fucosyltransferase which is active upon multiple substrates including Notch and EGFR and is important for post translational modification of receptors. Therefore, abnormal activity of the EGFR pathway is linked with infundibular keratinocyte differentiation and Th17 inflammatory pathways. The link to clinical disease activity is supported by reports of HS associated with the use of EGFR antagonists in oncology. Therefore, dysregulation of EGFR associated pathways secondary to GSC mutations may explain both the infundibular localization of HS, the involvement of the Th17 immune axis and cases of HS-like features in the setting of EGFR antagonism.

5.2 The evidence and proposed mechanisms for follicular rupture

Follicular rupture is proposed as the primary mechanism that follicular occlusion leads to diffuse dermal inflammation in HS. The histological evidence for follicular rupture is largely based upon findings from observational studies which show both dense peri-follicular and intrafollicular inflammation which discontinues in the follicular epithelium in affected tissue. Longstanding disease often has a noticeable absence of follicular and adnexal structures replaced with dense inflammatory infiltrates and scarring consistent with the known profound dermal inflammation but the mechanisms and process of follicular rupture are poorly understood.

Danby et al. documented PAS staining of the basement membrane zone (BMZ) in lesional HS tissues, and identified decreased staining compared to healthy controls. The authors proposed that defects or thinning of the BMZ may predispose the follicle in HS to rupture, with subsequent spillage of intrafollicular contents into the dermis stimulating the inflammatory cascade. The authors point to reduction in PAS staining to support this claim. In examination of the histological images, the PAS positive material measures approximately 60 μm in diameter which would be consistent with the thickness and morphology of the fibroreticular lamina which exists surrounding the basal lamina. The thinner dense staining (<10 μm diameter) would be consistent with the basal lamina (which appears intact). Other studies have not identified a reduction in desmosomal or hemidesmosomal components by IHC in HS specimens suggesting conflicting evidence using different methodologies. While the presence of epithelial discontinuities in HS follicles is not disputed, the elevated levels of matrix metalloproteinases (MMP2 and MMP3) and inflammatory cells may be implicated in the reduction of the thickness of the fibroreticular lamina. Therefore, further IHC staining and electron microscopy studies are needed to definitively establish the role of BMZ dysfunction as a pre-disposing mechanism in follicular rupture.

The mechanisms of follicular rupture in HS remain obscure. Occluded follicles in other conditions (such as epidermal inclusion cysts) is testament to the potential size intrafollicular collections may progress to before rupture. However, the early presence of inflammation in HS lesions may suggest an inflammation-related mechanism which is well-documented to disassemble the BMZ as part of the wound healing process. Epithelial-mesenenchymal transition (EMT) pathways play a role in the general wound healing process and have also been noted in the transcriptomic study of tissue from HS patients. This may also account for the presence of keratin staining cells in the dermis of HS sections suggesting desmosomal components by IHC in HS specimens and the development of dural tunnels. These EMT-associated signaling routes have also been identified in malignancy and wound healing processes and are thought to play a role in the metastatic potential of malignancy as well as the pathogenesis of longstanding wounds. Follicular rupture, therefore, may be more accurately considered as a process of “follicular disassembly” which is precipitated by chronic inflammatory changes via EMT and abnormal extracellular remodeling wound healing programs.
epithelium and reflect the structure of the overlying epidermis. These fibroblast processes are mediated via PDGF-α mediated signaling has been demonstrated in transcriptomic data from HS-associated fibroblasts. These fibroblast-derived signals are known to be secondary to inflammation-mediated epigenetic modifications and it is thus reasonable to assume that the development of dermal tunnels is an inflammatory process. However, once these tunnels are established, the CXCL1/8 gradient established across the epithelium (including tunnels) results in transepithelial neutrophil trafficking and NET formation in tunnel lumen. This results in development of the infiltrative proliferative gelatinous mass (IPGM) and biofilm formation in HS tunnels. Consequently, this provokes the recruitment of additional inflammatory cells to surround these dermal tunnels, contributing to the ongoing cycle of ongoing and severe inflammation and drainage. Therefore, rather than an end stage phenomenon, dermal tunnels are an inflammation driven process resulting in the development of active inflammatory organs contributing to the perpetuation of dermal inflammation in established disease.

7 | CONCLUSIONS

The available histological and molecular evidence suggest inflammation is a central component to the pathogenesis of HS. The current pathogenic paradigm of follicular occlusion as the "primem movens" in HS pathogenesis relegates inflammation as a secondary phenomenon and is not in keeping with the available evidence. The same evidence used to support the follicular occlusion paradigm is just as valid in supporting the concept of HS as a primarily inflammatory disorder with follicular occlusion a secondary event. Placing inflammation as the primary driver of disease provides a scaffold for testable hypotheses regarding polygenic risk loci for the development of HS; drug-induced causes of HS; the development of dermal tunnels and the IPGM which are currently poorly integrated into the follicular occlusion model of HS. Removing follicular occlusion as the primary driver of HS recalibrates the focus of therapy to addressing the inflammatory nature of the disease. While follicular occlusion is associated with HS, the evidence suggests that occlusion does not exclusively occur before inflammation. Realigning the pathogenic paradigm with the molecular evidence is essential to enable exploration of novel interventions and therapeutics for this debilitating disease.

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