Hidradenitis Suppurativa Tunnels: Unveiling a Unique Disease Entity

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Hidradenitis suppurativa tunnel structures lined with epithelium within the dermis are unique features of advanced disease stages that significantly impair patients' QOL. The presence of hidradenitis suppurativa tunnels is associated with a decreased likelihood of achieving a clinical response, even when receiving biological therapy. The cellular and molecular mechanisms underlying tunnel formation and pathology are only partially understood, which hampers the development of more effective targeted therapies. Tunnels create a unique microenvironment that drives a vicious cycle of hidradenitis suppurativa inflammation, with tunnel keratinocytes exhibiting an activated phenotype characterized by distinct gene expression signatures. In this review, we summarize the current literature and discuss aspects of the pathophysiology of tunnels, including the role of hair follicle epidermal stem cells in tunnel formation, potential role of fibroblast-mediated epithelial–mesenchymal transition, role of dermal papilla fibroblasts, and aberrant proinflammatory repair response contributing to the observed fibrosis and scarring. Finally, tunnel structures are characterized by unique microbial dysbiosis and an overabundance of Gram-negative anaerobes that are not targeted by current therapeutics. In addition to outlining the possible mechanisms of tunnel formation, we provide perspectives on the translation of current knowledge into more effective treatment approaches for patients with hidradenitis suppurativa tunnels.

Keywords: Epidermal stem cells, Hidradenitis suppurativa, Microbiome, Tunnels, Wound healing

INTRODUCTION

Hidradenitis suppurativa (HS) is a common chronic inflammatory skin disease that manifests systemically. HS is defined by its progressive course, proclivity to intertriginous areas, and unique underlying pathophysiology, which leads to nodules, abscesses, and tunneling wounds.

Tunnels characterized by a cylinder of keratinocytes with a central lumen within the dermis are unique to HS, with similar structures found in inflammatory conditions, such as dissecting cellulitis and severe acne conglobata (Figure 1). The presence of tunnels is often synonymous with the release of seropurulent malodorous discharges (Navrazhina et al, 2021). Emerging evidence suggests that tumors are an active source of inflammation in HS and contribute to disease progression (Navrazhina et al, 2021). Clinically, tunnels upstage disease severity in validated measures, such as the Hurley staging, International Hidradenitis Suppurativa Severity Score System, and Hidradenitis Suppurativa Physician's Global Assessment (Kimball et al, 2012; Zouboulis et al, 2017, 2015), mainly driven by the impact of tunnels on patients living with HS (Kimball et al, 2018; Krajewski et al, 2021; Matusiak et al, 2018; Onderdijk et al, 2013; Von der Werth and Jemec, 2001; Wolkenstein et al, 2007) (Table 1). An emerging alternative scoring system, the Hidradenitis Suppurativa Investigator Global Assessment, uses a composite score that incorporates abscesses, nodules, and draining and nondraining tunnel counts (Garg et al, 2023), whereas the Hidradenitis Suppurativa Clinical Response used in clinical trials focuses on the change in the number of inflammatory nodules, abscesses, and draining tunnels (Kimball et al, 2016a). These discrepancies in grading systems indicate that tunnels and nodules do not carry the same clinical significance and provide additional evidence that tunnels are distinct disease features.

Tunnels are typically resistant to medical therapies, which leads to higher morbidity. Patients with HS with tunnels often require more medical intervention and frequently undergo surgery compared with those without tunnels, resulting in higher patient costs and increased healthcare demands. Depression, anxiety, and sexual dysfunction are prevalent comorbidities in patients with HS that increase with disease severity and significantly affect the patient's QOL

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Abbreviations: DC, dendritic cell; DP, dermal papilla; ECM, extracellular matrix; EMT, epidermal–mesenchymal transition; ESC, epidermal stem cell; FDA, Food Drug Administration; G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; HS, hidradenitis suppurativa; K, keratin; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap

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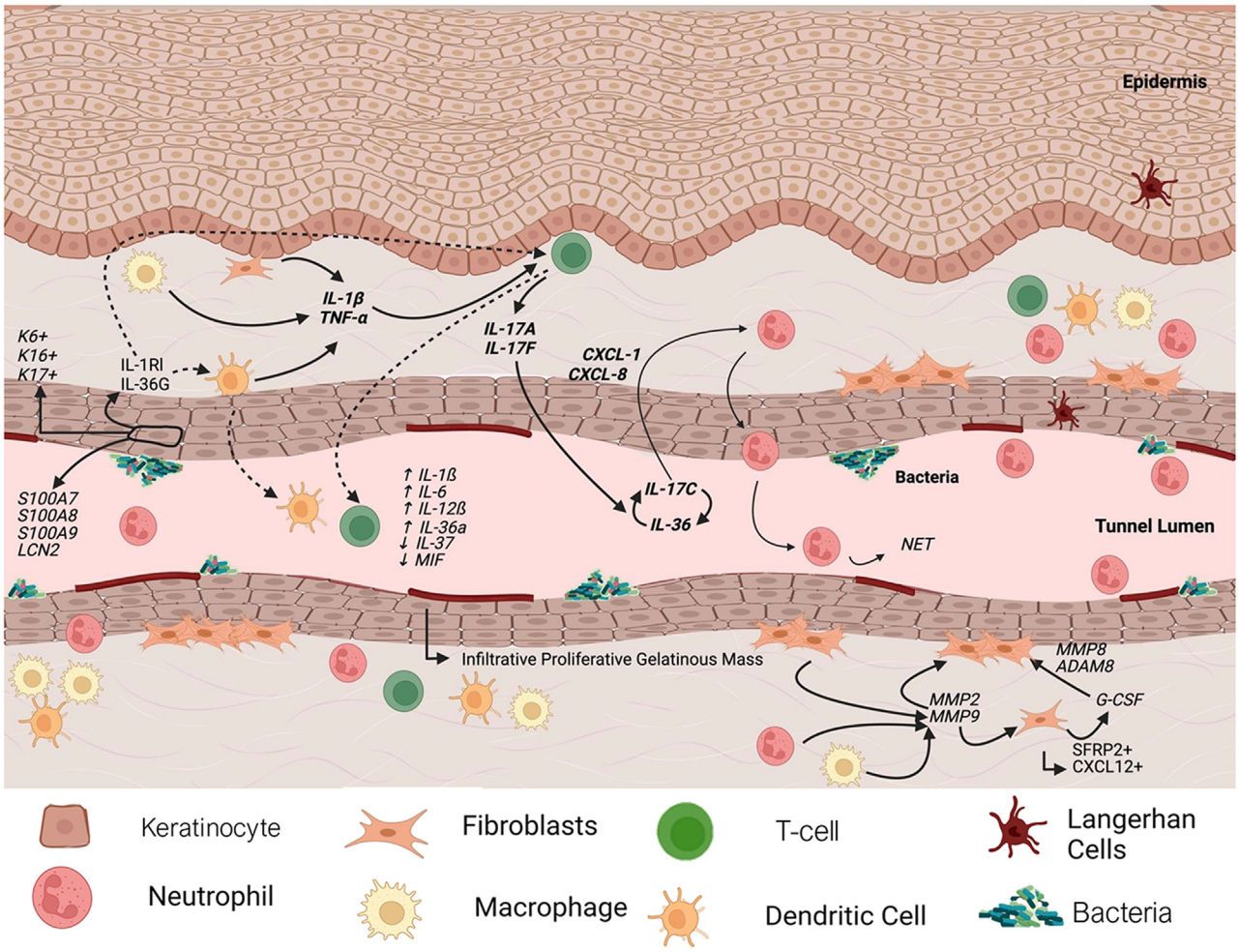

Figure 1. HS tunnels are active drivers of disease chronicity. HS lesions display psoriasiform hyperplasia of the overlying epidermis. Tunnels, characterized by dermal keratinocytes forming a central lumen, exhibit heightened infiltration of T cells, dendritic cells, and neutrophils, along with increased levels of neutrophil-associated factors, B cell–related cytokines, and NETs. The tunnel lumen is lined with an IPGM, containing inflammatory cells and cytokines that promote immune cell infiltration and NET formation. Microbial dysbiosis and subsequent biofilm formation within the tunnel also promote inflammation. Tunnel keratinocytes are characterized by increased expression of activation markers: K6, K16, and K17; alarmins (S100A7, S100A8, and S100A9); and neutrophil gelatinase-associated LCN2. HS fibroblasts express various proinflammatory cytokines and G-CSF, which activates proteases MMP8 and ADAM8, contributing to uncontrolled fibrosis and inflammation. G-CSF, granulocyte colony-stimulating factor; HS, hidradenitis suppurativa; IPGM, infiltrative proliferative gelatinous mass; K16, keratin 16; K17, keratin 17; K6, keratin 6; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap.

(Kimball et al, 2018). Despite revolutionizing the treatment paradigm for HS, emerging biological medications still fail to treat tunnels (Frew et al, 2021a, 2020; Kimball et al, 2023), with excisional surgery being the remaining option. Hence, the wide therapeutic gap highlights our limited understanding of tunnel pathophysiology.

In this paper, we review the current literature on the epidemiology, molecular and cellular pathology, and microbial dysbiosis in relation to HS tunnels, emphasizing the much-needed investigation of the mechanisms of tunnel formation and persistence. We reflect on the current and future research tailored toward the development of tunnel-directed therapeutics as the next frontier for improving outcomes in HS.

HS TUNNELS: EPIDEMIOLOGY AND CLINICAL ASSESSMENT

Typically, HS manifests clinically during adolescence and affects both sexes (Di Cesare et al, 2022; Ingram et al, 2018; Vaiopoulos et al, 2020). Accurate determination of the overall prevalence of HS remains challenging, with current population studies estimating a worldwide prevalence of 0.40% (95% confidence interval = 0.26–0.63%) (Jfri et al, 2021). HS is also frequently misdiagnosed, leading to well-characterized diagnostic delays ranging from 7 to 10 years worldwide (Garg et al, 2020, 2017b; Saunte et al, 2015). Women are the most affected by HS in Western countries (Garg et al, 2017b; Ingram et al, 2018), with a reported 3:1 ratio to men (Garg et al, 2017a), whereas a male predominance is present in Asia (Chandran et al, 2021; Omine et al, 2020). Furthermore, evidence suggests that the specific sex distribution of HS tunnels differs. Larger clinical studies have shown that the sex ratio in patients with moderate-to-severe disease is close to 1:2 (Bechara et al, 2021; Kimball et al, 2023, Kimball et al, 2016b; Kirney et al, 2023). Sex-specific tunnel involvement patterns exist: females commonly exhibit axillary, inframammary, and inguinal involvement, whereas males typically have buttock, perianal, or atypical involvement (Martorell et al, 2015).

Table 1. Summary of the Different Staging and Scoring Systems for HS, Including their Strengths and Limitations in Recognizing Severity of Tunnels

Staging/Scoring System	Description	Strengths	Limitations
Hurley staging	Classifies HS into 3 stages on the basis of abscesses, scarring, and tunnel formation	Simple and common classification of disease severity	Does not accurately reflect the burden of tunnels. Mild or moderate disease may be overrepresented
Hidradenitis Suppurativa Physician Global Assessment	Categorizes HS into 6 levels of severity (clear, minimal, mild, moderate, severe, very severe) on the basis of nodules, abscesses, and tunnels	Provides a detailed severity scale	Fails to differentiate nodules and abscesses from tunnels, potentially underestimating disease severity
International Hidradenitis Suppurativa Severity Score System	Scores disease severity on the basis of the number and type of lesions, including tunnels. A tunnel score of 4 indicates moderate disease.	Recognizes the impact of tunnels on disease burden	The system might not account for all aspects of disease severity beyond lesion count
Hidradenitis Suppurativa Investigator Global Assessment	Rates severity from 0 to 5 based on abscesses, nodules, and tunnels in affected regions	Generates a composite score incorporating various lesion types and locations	Overlooks pain, drainage, and odor associated with tunnels
Hidradenitis Suppurativa Clinical Response	Measures response on the basis of clinical improvements and reduction in lesions	Shows significant convergence with DLQI, indicating better alignment with patient QOL	Provides count of draining tunnels, not the total number of tunnels

Abbreviations: HS, hidradenitis suppurativa; DLQI, Dermatology Life Quality Index.

Research on HS severity among different races and ethnicities is limited; however, Black patients are more likely to have tunnels than White patients (Kirney et al, 2023). Although racial and ethnic disparities pertaining to the presence of tunnels may exist, biological versus environmental contributors to tunnel pathogenesis among different racial and ethnic groups have not yet been explored in depth.

On physical examination, HS tunnels present as tender, linear subcutaneous tracts that may have 1 or more cutaneous openings on the skin surface or blind ends (Frew et al, 2021a,b; Scheinfeld, 2014). They can also form fistulas that connect to hollow organs. Variable levels of malodorous drainage, after manual palpation of the surrounding soft tissue, can clinically distinguish tunnels from draining nodules or abscesses. Additional clinical clues are the concomitant presence of inflammatory erythematous papules or nodules, superficial or subcutaneous abscesses, double-headed pseudo-comedones, and mild to cigarette-like follicular scarring. Chronic tunnels are often surrounded by painful erythematous plaques, suggesting an underlying subcutaneous extension of the visualized tunnel. Pathognomonic rope-like scarring with dermal contractures and open ulcerations indicates disease chronicity and progression.

Current data suggest a high burden and prevalence of tunnels, mostly due to delayed diagnosis and underdiagnosis. This is reflected in HS grading systems limited by intergrader variability (Martorell et al, 2019a; Thorlacius et al, 2019), especially in tunnel identification (Table 1). Because tunnels are dermal structures, proper assessment of their length and depth is challenging, both visually and with manual palpation. Ultrasound techniques can objectively assess tunnel depth and severity (Elkin et al, 2020; Martorell et al, 2019b; Napolitano et al, 2019; Varkey et al, 2014; Wortsman and Jemec, 2007; Wortsman and Wortsman, 2010; Wortsman et al, 2016, 2013); however, ultrasound is still not widely adopted for tunnel diagnostics and evaluation, further contributing to underdiagnosis and lack of proper disease management. The emergence of higher-frequency portable ultrasound devices is encouraging, and if adopted in the clinic, a meaningful change in management could be achieved (Weigelt et al, 2021).

HS TUNNELS CONTRIBUTE TO PROLONGED INFLAMMATION

HS tunnels have previously been viewed as inert fibrotic end-stage products that do not contribute to disease pathogenesis (Goldburg et al, 2020a, 2020b; Vossen et al, 2018). However, recent studies have challenged this hypothesis and established that epithelialized tunnels play an active role in disease propagation as major drivers of HS inflammation (Navrazhina et al, 2021) (Figure 1). The tunnel epidermis recapitulates the psoriasiform hyperplasia of the overlying epidermis; however, significant differences exist in the tunnel immune cell profiles and associated proinflammatory mediators compared with those in both the overlying HS epidermis and chronic inflammatory psoriatic epidermis (Adawi et al, 2025; Navrazhina et al, 2021).

Although skin-resident innate lymphoid cells play an important role in controlling the commensal microbiota of the pilosebaceous unit under physiological conditions (Kobayashi et al, 2019), HS is characterized by a robust, progressive, and dysregulated inflammatory cellular milieu. The immune landscape changes in a temporospatial manner during HS pathogenesis, where nascent lesions are characterized by neutrophilic inflammation and abscess formation, along with the recruitment of macrophages, monocytes, dendritic cells (DCs), T cells, and B cells (van der Zee et al, 2012; van Straalen et al, 2024a). HS tunnels are characterized by an increased infiltration of T cells, DCs, and neutrophils compared with HS lesions without tunnels, accompanied by an increase in neutrophil-associated factors, B cell–associated cytokines and chemokines as well as mediators that promote neutrophil chemotaxis (Navrazhina et al, 2021) (Figure 1). Furthermore, compared with the overlying epidermis, HS tunnels display increased numbers of neutrophil extracellular traps (NETs) (Byrd et al, 2019; Oliveira et al, 2025, 2023; Navrazhina et al, 2021), web-like formations expelled by activated neutrophils that consist of

DNA fibers, histones, and antimicrobial proteins, and function by trapping and subjecting pathogens to a concentrated and lethal dose of effector proteins (Sawaya et al, 2022). In addition, the tunnel lumen is lined with an infiltrative proliferative gelatinous mass, a reddish, jelly-like substance that adheres to the tunnel epithelium and consists of various inflammatory cells and associated with cytokines and growth factors that cumulatively promote immune cell infiltration, NET formation, and tissue remodeling (Kidacki et al, 2019; Margesson and Danby, 2014), suggesting further amplification of tunnel-driven inflammation.

On the basis of the current literature, IL-17–producing T cells are thought to be a major driver of HS tunnel development (Navrazhina et al, 2021). Compared with the overlying epidermis, HS tunnels display increased expression of IL-17A, IL-17B, IL-17C, and IL-17F, whereas blocking IL-17 decreases tunnel drainage in patients (Kim et al, 2023; Navrazhina et al, 2021). HS tunnels also demonstrate higher expression of IL-36α, further driving T-cell proliferation. It was also shown that secretion of IL-17C and IL-36α from epithelialized tunnels (Navrazhina et al, 2021) could lead to increased expression of proinflammatory chemokines CXCL1 and CXCL8 responsible for amplification of neutrophil chemotaxis (Figure 1). In addition, single-cell RNA-sequencing data revealed that T helper 17 cells in lesions comprising tunnels had lower levels of IL-23R and higher levels of IL-1R1 than in psoriasis, another IL-17–driven disease, suggesting an alternative HS unique activation pathway most likely driven by IL-1β and not by IL-23 as in psoriasis (Kim et al, 2023, 2021). Further investigation found that semi-immature DCs, tunnel-derived keratinocytes, and fibroblasts were main source of IL-1β and IL6, which are known to prevent immune suppression by T regulatory cells (Goodman et al, 2009; Kim et al, 2023).

B cells and plasma cells have also been implicated in HS formation, with increased localization surrounding tunnels compared with that of the overlying epidermis (Gudjonsson et al, 2020). Specifically, $CD20^+$ B cells and $CD138^+$ plasma cells were found to be concentrated around tunnels. In addition to the prominence of B cells in HS lesional tissues, ectopic germinal centers and follicular DCs can also be detected in advanced-stage HS (Macchiarella et al, 2023). Interestingly, BAFF (also known as TNFSF13B) released by neutrophils was found to be upregulated more in earlier HS lesions than in lesions with tunnels (Sabat et al, 2023), suggesting that B-cell activation in the vicinity of tunnels occurs independently in ectopic germinal centers. Cumulatively, the increased load of immunocytes and inflammatory mediators in and around the tunnels provides strong evidence that tunnels play an active role in driving HS inflammation at advanced stages of the disease, thereby contributing to disease chronicity and recurrence.

THE ROLE OF KERATINOCYTES IN PATHOGENESIS OF TUNNELS

Although current research has provided the first line of evidence regarding the role of tunnels in the pathogenesis of HS (Navrazhina et al, 2021), studies focusing on tunnel formation remain limited. One widely accepted hypothesis involves hair follicle disruption as the inciting event of epithelized tunnel formation. The hair follicle is a unique appendage often described as a miniorgan (Langan et al, 2015). The hair follicle at the beginning of the anagen phase consists of dermal papilla (DP) fibroblasts at the distal base, a bulge region that contains epidermal stem cells (ESC), inner and outer root sheaths made up of undifferentiated keratinocytes, and a sebaceous gland that connects to the root sheath (Figure 2). Positive staining for trichohyaline, a protein that characterizes the inner root sheath of hair follicles, in HS tunnels has been proposed to indicate hair follicle involvement in tunnel formation (Navrazhina et al, 2021). One hypothesis describes the infiltration of squamous epithelium of the hair follicle, denoted as "tendrils," into surrounding tissues that form cysts, which eventually rupture to form epithelialized tunnels (Dunstan et al, 2021). Hair follicle rupture due to inflammation occurs in other dermatological diseases, such as complex pilonidal disease, yet epithelialized tunnels remain a unique feature of HS, suggesting additional contributing mechanisms (Cuellar et al, 2020; Khanna and Rombeau, 2011).

It is established that keratinocytes of the outer root sheath of the hair follicle display a proinflammatory signature in HS lesions, with significant secretion of IL-1β, IL10, CCL5, and S100A7 (Frew, 2020; Kashyap et al, 2022; Zouboulis et al, 2020). Keratinocyte dysregulation in HS is primarily thought to occur as a result of activation of the IL-17 and IL-23–T helper 1 pathways. Dysregulated keratinocytes are also characterized by the aberrant production of antimicrobial peptides and proinflammatory cytokines that recruit CD4 + T cells, contributing to the immunopathogenesis of the disease (Chopra et al., 2022). Keratinocytes lining the tunnel lumen have an activated phenotype characterized by keratin (K)6, K16, and K17 expression, which may contribute to tunnel protrusion, because K6, K16, and K17 are also markers of migrating keratinocytes (Adawi et al, 2025; Navrazhina et al, 2021; Pastar et al, 2014). However, the migratory phenotype of tunnel keratinocytes may be a consequence of the epidermal–mesenchymal transition (EMT), which is hypothesized to occur in advanced-stage HS (Flora et al, 2023; Frew et al, 2019; Shishido-Takahashi et al, 2024). EMT has been shown to be triggered in epithelial cells during the wound-healing process and neoplastic progression. In addition, hepatocyte GF (HGF), which is overexpressed by HS fibroblasts, triggers the activation of EMT-related genes and pathways in keratinocytes, including *TWIST2* and the mesenchymal marker vimentin. HGF-induced genes were found to be significantly upregulated in HS lesions with tunnels (Shishido-Takahashi et al, 2024).

Differences in epidermal and tunnel keratinocyte transcriptomes are yet to be fully elucidated. A recent study compared the single-cell transcriptomic profiles of HS lesional epidermis with those of HS tunnels and revealed a unique gene expression signature in HS tunnel keratinocytes (Kim et al, 2023). In addition to K6, K16, and K17 overexpression, keratinocyte-derived alarmins S100A7, S100A8, S100A9, and neutrophil gelatinase–associated LCN2 were induced in HS tunnels, providing further evidence that tunnel keratinocytes have an acute wound-like phenotype (Eckert et al, 2004; Wolk et al, 2017). However, Dajnoki et al (2022) reported significant LCN2 expression in lesional

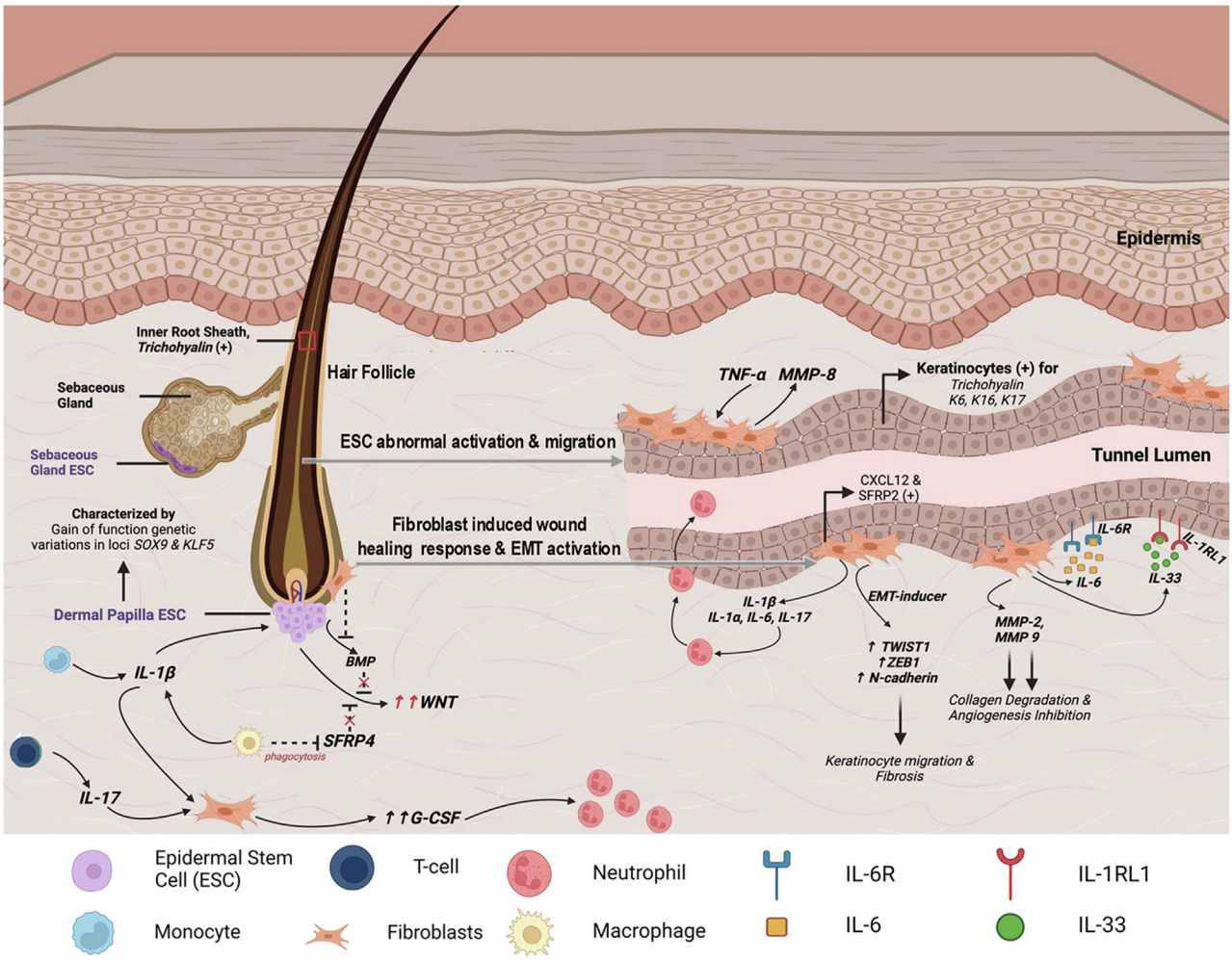

Figure 2. The proposed and interconnected cellular processes driving tunnel formation and propagation. Epithelial stem cell aberrant activation and keratinocyte migration are hypothesized to drive tunnel formation. GWASs have found a genetic association between the *SOX9* and *KLF5* gene loci both important in regulating ESC function. DP fibroblasts and ESCs interact in a coordinated manner to maintain tissue homeostasis and support cutaneous regeneration through WNT and BMP signaling; however, chronic WNT signaling, driven by macrophages that phagocytize the WNT inhibitor SFRP4, is associated with excessive fibrosis in HS. Fibroblasts-induced wound-healing response and EMT activation are hypothesized to contribute to tunnel formation: HS tunnels demonstrate elevated EMT signals, including TWIST1, ZEB1, and N-cadherin. Tunnels are also characterized by a unique population of CXCL12+ and SFRP2+ fibroblasts. An increased expression of inflammatory mediators and proteinases likely contribute to tunnel propagation by causing ECM remodeling and immune cell recruitment. DP, dermal papilla; ECM, extracellular matrix; EMT, epidermal–mesenchymal transition; ESC, epidermal stem cell; HS, hidradenitis suppurativa; MMP, matrix metalloproteinase.

epidermis, suggesting that LCN2 is not a unique feature of the tunnel epidermis. In addition, the invasive and migratory features of keratinocytes in HS tunnels remain only partially understood, and the most recent study has identified an overall overlap with well-differentiated invasive squamous cell carcinoma (Adawi et al, 2025).

HS tunnel keratinocytes also express increased IL-17C, IL-1α, IL-1ß, and IL-6, further amplifying T-cell–driven response (Kim et al, 2023) and supporting the concept of epithelialized tunnels as a major driver of HS inflammation. On the basis of these characteristics, it can be postulated that tunnels reflect an acute, inflamed, and often colonized wound that forms deep in the dermis, whereas the epidermis above the tunnel remains relatively quiescent (Figure 1). Crosstalk between tunnel keratinocytes and inflammatory cells is the key to understanding the pathophysiology of this advanced stage of the disease, especially in patients who fail to respond to Food Drug Administration (FDA)–approved anti–IL-17 and anti-TNF therapy.

Hair follicle stem cells have also been proposed to participate in tunnel formation because they play a critical role in cutaneous tissue repair and hair follicle maintenance (Guenin-Mace et al, 2023; Naik et al, 2017). ESCs exist in 3 hair follicle microenvironments: the bulge of the hair follicle, the base of the sebaceous gland, and the basal layer of the interfollicular epidermis (Fuchs, 2015; Hsu and Fuchs, 2022; Ojeh et al, 2015) (Figure 2), with an additional myoepithelial niche residing in sweat glands (Biedermann et al, 2010; Gonzales and Fuchs, 2017; Lu et al, 2012). ESCs are known to function in the regeneration of skin and appendages as well as in wound healing (Lu et al, 2012; Naik and Fuchs, 2022; Pastar et al, 2014). Furthermore, IL-1β, which is

highly activated in HS and enhances response to injury (Naik et al, 2017), may drive the inflammatory memory of ESCs in HS, leading to their aberrant activation due to repeated injury by hair follicle rupture. The role of ESC from the pilosebaceous–apocrine unit in tunnel formation has also been proposed (Marohn et al, 2020[1]) and requires further in-depth studies. Recent GWASs have identified an association between SOX9 and KLF5, which are both important for ESC function and the risk of HS (Khan and Petukhova, 2023; Sun et al, 2023). KLF5 regulates ESC, and its expression must be tightly controlled, whereas aberrant KLF5 expression may lead to disruption of the skin barrier if deleted or hyperproliferation, hyperkeratosis, and follicular occlusion if overexpressed in murine models (Lyu et al, 2022; Sun et al, 2023; Sur et al, 2006), as in HS. However, a recent study provided evidence that barrier disruption may not be an important primary driver of HS, necessitating further understanding of the role of barrier breach in disease pathogenesis (Somogyi et al, 2023). Whereas KLF5 functions as a regulator of ESCs, SOX9 is the primary regulator of hair follicle stem cells, follicular differentiation, and keratinocyte proliferation. SOX9 is overexpressed in conditions such as psoriasis and nonmelanoma skin cancers, which are characterized by the abnormal differentiation and proliferation of keratinocytes (Kadaja et al, 2014; Lyu et al, 2022; Shi et al, 2013; Vidal et al, 2005). In addition, SOX9 may be involved in the dysregulation of the extracellular matrix (ECM) in HS through the induction of matrix metalloproteinase (MMP)1 and MMP2 and the promotion of inflammation through the induction of IL-8 (Luo et al, 2018). Although GWAS findings may also implicate the involvement of SOX9 and KLF5 deregulation in tunnel formation, the deregulation of the ESC niche in HS; ESC–immune response crosstalk (Figure 2); the interplay of specific pathways and regulatory factors, including but not limited to SOX9 and KLF5; and their role in tunnel formation remain to be determined.

FIBROBLASTS: MAJOR CONTRIBUTOR TO TUNNEL PATHOGENESIS

Fibroblasts often overlooked as "bystanders" are emerging as key players in tunnel pathogenesis and therefore deserve future attention from both mechanistic and therapeutic aspects. Intimate crosstalk between keratinocytes and fibroblasts is necessary for skin homeostasis and appropriate physiological response to stressors (Russo et al, 2020). The extensive scarring and fibrosis seen in HS tunnels and recent data demonstrating the upregulation of fibroblast signatures in both lesional and nonlesional HS tissue (Karma et al, 1986) point to fibroblasts as one of the early drivers of the disease. Although previous research efforts have mostly focused on deciphering the inflammatory response in advanced-stage HS, elucidating the role of fibroblasts in disease pathogenesis and their interplay with keratinocytes and immune cells is paramount for understanding HS progression, including tunnel formation and associated fibrosis, a hallmark of advanced HS.

Traditionally, fibroblasts are known for their role in producing ECM components, including collagen and elastic and reticular fibers, which support the dermis and overlying epidermis in tissue homeostasis, and pathologically for their role in fibrosis and scarring (Brown and Krishnamurthy, 2025). Fibroblasts display remarkable heterogeneity in their developmental origins, cell lineages, and local tissue microenvironments (Bartoschek et al, 2018; Deng et al, 2021; Driskell and Watt, 2015; Lynch and Watt, 2018; Talbott et al, 2022). More recent studies have documented the complexity of the diverse roles and plasticity of fibroblast phenotypes in the skin, including maintaining local ECS niches, regulating the tensile strength of the dermis in response to wounding, recruiting immune cells, and demonstrating the capacity to switch cell types in response to local microenvironmental cues (Gomes et al, 2021; Plikus and Krieg, 2021). In this section, we discuss and propose several mechanisms through which fibroblasts may contribute to advanced disease stages and HS tunnel formation, including (i) triggering EMT, (ii) deregulated wound healing response, and (iii) the potential role of DP fibroblasts in the early stages of tunnel formation (Figure 2).

Although HS is not classically defined as a wound-healing disorder, follicular rupture and subsequent tissue repair occurring in HS require a robust tissue repair response (Coates et al, 2019). Thus, aberrant healing signaling cascades are likely to be involved in driving advanced disease and HS tunnel formation. Extensive fibrosis seen in HS lesions is also well-documented in chronic wounds, largely coordinated by TGFß and myofibroblasts (Pastar et al, 2023; Stone et al, 2020).

The complex role of fibroblasts in HS is reflected in the multiple signaling features that have been characterized. A recent single-cell RNA-sequencing study indicated that HS fibroblasts are the main source of IL-6 and IL-33, which likely interact with IL-6R and IL-1RL1, respectively, in tunnel keratinocytes (Kim et al, 2023), further amplifying keratinocyte-driven inflammation in HS tunnels. IL-6 also synergizes with IL-1β to maintain cytokine expression in T helper 17 cells, contributing to additional promotion of inflammation through paracrine IL-1/IL-6 loop. Importantly, IL-6, necessary for the inflammatory and proliferative phases of wound healing (Johnson et al, 2020), is also implicated in uncontrolled fibrosis (Johnson et al, 2020) and likely contributes to HS tunnel pathogenesis in a similar manner. MMP8 expression, stimulated by proinflammatory TNFα, is increased specifically in HS fibroblasts, thus contributing to ECM remodeling (Molnar et al, 2020; Tsaousi et al, 2016). HS fibroblasts are also the main contributors of granulocyte colony-stimulating factor (G-CSF) production, known for its healing-stimulating properties (Barrientos et al, 2014; Cruciani et al, 2005), and are activated by IL-17 and IL-1ß expressed in HS tunnels (Wolk et al, 2021). Higher levels of G-CSF found in HS than in other chronic inflammatory skin conditions may contribute to an amplified vicious cycle of inflammation, resulting in the activation of proteases MMP8 and ADAM8 and subsequent ECM remodeling, contributing to fibrosis. These findings support the notion that an acute wound healing response occurs in HS. A recent study showed distinct CXCL12+ and SFRP2+ fibroblast populations in HS

[1] Marohn M, Lin M-j, Yu W-w, Mendoza CM, Remark J, Khodadadi-Jamayran A, et al. Defining epidermal stem cell fate infidelity and immunogenicity in hidradenitis suppurativa at the single-cell resolution. bioRxiv 2020.

tunnels (Flora et al, 2023). In contrast to tunnels, chronic HS lesions are characterized by a population of SFRP4+ and CXCL13+ fibroblasts, indicating a highly structured inflammatory signature through robust stromal–immune cell crosstalk and the secretion of chemoattractants that recruit myeloid and B cells and activate fibrosis through Hippo signaling (van Straalen et al, 2024). Although previous studies have been performed on tissue samples, future studies are needed to uncover and isolate fibroblast subpopulations specific to the tunnel niche that may contribute to disease progression, activation of the wound-healing phenotype, and fibrosis.

Furthermore, during physiological wound healing, fibroblasts secrete promigratory signals to the leading edge of wound keratinocytes, allowing them to migrate and pull their adjoining neighbors across the granulation tissue toward the wound center (Pastar et al, 2014; Stone et al, 2016), which requires ECM remodeling achieved mainly by protease activity. Keratinocyte migration requires an EMT genetic switch, whereby an epidermal keratinocyte transforms into a more fibroblast-like or mesenchymal phenotype, depolarizing the basal epidermis, disconnecting adjoining cells, and allowing cell movement (Kalluri and Weinberg, 2009), which may also play a role in the formation of HS tunnels. Similarly, HS lesions show a robust increase in MMP2 and MMP9, major ECM remodelers in the skin (Sanchez et al, 2019). Interestingly, HS tunnels demonstrated elevated EMT signals, including *TWIST1, ZEB1*, and N-cadherin, compared with HS lesions without tunnels and healthy control tissues. The use of systemic fostamatinib, a splenic tyrosine kinase inhibitor, administered over 4 weeks led to a significant reduction in the expression of genes related to fibrosis, inflammation, and EMT (Flora et al, 2023), suggesting the importance of therapeutic targeting of HS tunnel fibroblasts. It is also proposed that dysregulated stromal signaling in HS coupled with the EMT signals driven by HS tunnel fibroblasts may also contribute to higher incidence of aggressive squamous cell carcinoma observed in patients with long-term HS (Frew et al, 2019; Jourabchi et al, 2017; Juviler et al, 2019) because cancer-associated fibroblasts are known as main drivers of epithelial tumor invasiveness (Liu et al, 2019; Stone et al, 2016; Szabo et al, 2023; Wiechec et al, 2021), again underscoring the need for fibroblast-targeted therapeutics.

DP fibroblasts at the base of the hair follicle are indispensable for hair follicle regeneration (Ma et al, 2022); however, their role in HS pathogenesis and tunnel formation remains unknown. DP and ESCs constantly interact in a temporally and spatially organized manner, maintaining tissue homeostasis and participating in cutaneous barrier and regeneration. The WNT ligand secreted by bulge ESCs activates the proliferation of dermal fibroblasts and formation of DP. However, chronic WNT signaling, stimulated by phagocytosis of the WNT inhibitor SFRP4 by macrophages, is implicated in uncontrolled fibrosis in HS (Gay et al, 2020). DP cells secrete local extracellular vesicles that induce ESC to regenerate the hair follicle through the nonconventional WNT ligand norrin (le Riche et al, 2019), whereas clathrin-mediated endocytosis, implicated in the uptake of exosomes, has recently been identified as induced in the tunnel epidermis (Adawi et al, 2025). Given the importance of DP in regulating ESCs and their remarkable plasticity, it is tempting to speculate that genetic or epigenetic changes in these cells lead to erroneous ESC activation during HS and subsequent tunnel formation (Figure 2). Future studies of the initial stages of HS and tunnel formation may reveal the role of DP fibroblasts in the pathogenesis of HS tunnels.

MICROBIAL DYSBIOSIS IN HS TUNNELS

Immune cell dysregulation is accompanied by microbial dysbiosis in HS tunnels. However, the role of microbial imbalance in HS remains unclear, with debates over whether it is a primary or secondary event (Chopra et al., 2022). Bacteria have been shown to be spatially associated with activated keratinocytes in HS tunnel tissue with the ability to induce keratinocyte inflammation, underscoring their importance in tunnel pathogenesis (Williams et al, 2024). However, a rare loss-of-function sequence variant, resulting in a deficiency in the antimicrobial peptide dermicidin, is hypothesized to contribute to microbial dysbiosis in HS as a consequence of disease pathogenesis (Tricarico et al, 2022). Further in-depth mechanistic and clinical studies are required to determine whether the skin microbiome contributes to or is a result of the underlying disease processes.

It is established that Gram-negative anaerobes dominate in chronic HS lesions and tunnels (Brook and Frazier, 1999; Gonzalez et al, 2025; Guet-Revillet et al, 2017, 2014; Jiang et al, 2021; Lapins et al, 1999; Ring et al, 2017a, 2017b; Riverain-Gillet et al, 2020). Loss of commensal abundance occurs with disease progression, which may enable the growth of pathogenic species, including obligatory anaerobes such as *Prevotella sp, Porphyromonas sp, Finegoldia magna, Fusobacterium sp, Parvimonas sp, Streptococcus sp*, and the facultative anaerobe *Staphylococcus sp* (Gonzalez et al, 2025; Guet-Revillet et al, 2017; Jiang et al, 2021; McCarthy et al, 2022; Nikolakis et al, 2017; Pardo et al, 2024). Deep biopsies from advanced HS showed a higher abundance of *Prevotella sp* and *Porphyromonas sp* than in the early stages, highlighting the distinct dysbiosis and differences between the external skin, tunnels, and various disease stages (Pardo et al, 2024). Importantly, *Porphyromonas sp* found in tunnels is known for its ability to trigger NETosis in chronic periodontal disease (Frew et al, 2019), and *F magna* can also trigger inflammation through the activation of neutrophils and associated NETosis (Neumann et al, 2020), indicating the role of the microbiome in driving the vicious cycle of HS inflammation (Chopra et al, 2022) (Figure 1). The most recent study utilizing keratinocyte in vitro and in vivo models of infection with Gram-negative anaerobes identified the induction of IL-17 and TNF pathways in response to keratinocyte treatment with heat-inactivated *F nucleatum* and *Prevotella sp*, further confirming the role of fastidious Gram-negative microorganisms in tunnel-driven inflammation (Williams et al, 2024).

Bacterial biofilm formation is also increased in tunnels, most likely contributing to subsequent antimicrobial resistance (Huynh et al, 2024; Wolk et al, 2020). Tunnels are thought to promote microbial dysbiosis due to the presence of keratin debris and hair fragments that enable bacterial attachment, which is the first step in biofilm formation (Chen et al, 2022; Chopra et al, 2022). The presence of biofilms and

the treatment of inaccessible bacterial niches in tunnels may also predispose patients to secondary colonization and perpetual invasion. Together with the high resistance to antibiotics confirmed in HS isolates (Bettoli et al, 2019), bacterial biofilms and dysbiosis represent an unaddressed issue for HS treatment. A recent study demonstrated that targeting HS tunnels with local antibiofilm therapy shifted microbiome dysbiosis, subsequently leading to diminished inflammation (Weigelt and Lev-Tov, 2021) and reducing the need for surgery, thus offering a new therapeutic avenue. Gaining greater insight into the interplay between tunnel-specific microbial dysbiosis and the impacted cellular processes is critical for understanding and treating patients with advanced HS.

CURRENT AND FUTURE TREATMENT STRATEGIES FOR HS TUNNELS

The treatment armamentarium of HS is wide, but no therapy, including FDA-approved TNF-α and IL-17 inhibitors, is consistently or widely effective for patients affected with HS tunnels (Kirby et al, 2014). Scarring fibrosis and variations in the structure and location of tunnels could impede systemic drug delivery to these lesions and partially explain the observed decrease in treatment response.

Both TNF-α and selective IL-17A inhibitors resulted in improvement in reduction of draining tunnels (Grant et al, 2010; Kimball et al, 2023, Kimball et al, 2016b). Bimekizumab, a mAb that inhibits both IL-17A and IL-17F, has recently been shown to produce clinically significant improvements in moderate-to-severe HS, affecting deep lesions and providing a promising treatment for tunnel inflammation (Glatt et al, 2021; Kimball et al, 2024). In addition, ongoing clinical trials investigating oral selective Jak-1 inhibitors have revealed promising results in patients with draining tunnels and decreased serum high-sensitivity C-reactive protein (Kirney et al, 2023). However, most patients enrolled in these clinical trials had early-stage disease, and the reduction in the total number of tunnels remains underreported (Kimball et al, 2023, Kimball et al, 2016b; Kirney et al, 2023). Additional emerging pharmacological therapies include IL-36R inhibitors and IFX-1; none of which have shown significant improvement in HS, despite their initial promise (Alavi et al, 2024; Zouboulis et al, 2021). Hence, surgery is the only current modality that provides patients with HS tunnels with a near-remission prognosis (Goldburg et al, 2020a) and improves outcomes in combination with biologics (Aarts et al, 2023; Bechara et al, 2021). Several surgical procedures are available, including intralesional steroid injections, incisions, and debridement. Deroofing is a commonly used, minimally invasive, and tissue-sparing technique that is highly effective in treating tunnels with a low recurrence rate (33%). It is 4.38-fold superior to wide excision (Ravi et al, 2022; van der Zee et al, 2010).

Clinicians frequently prescribe antibiotics to patients with HS; however, these treatments typically offer only temporary relief, mostly owing to their anti-inflammatory effects, rather than a cure (van Straalen et al, 2023b). Importantly, a high number of reported HS isolates that are resistant to empirically and widely used rifampicin, clindamycin, and tetracyclines (Bettoli et al, 2019) imposes a risk of secondary infections that may be amplified in patients on anti-inflammatory medications. Antibiotics that target anaerobic bacteria, including ertapenem, carbapenem, metronidazole, and nitroimidazole (Huynh et al, 2024; Kathju et al, 2012), could be effective against tunnel-specific bacteria; however, no current metagenomic or in vitro studies have identified susceptibility or antibiotic-resistant traits specific to the tunnel microbiome (Goldburg et al, 2020a; Grant et al, 2010; Kimball et al, 2023, Kimball et al, 2016b; Kirney et al, 2023). A novel minimally invasive procedure, involving the creation of a punch incision at each end of the tunnels under local anesthesia and daily flushing of the tunnel with an antibiofilm gel, has shown a resolution rate of 93% in tunnels by day 28, with an average healing time of 12 days (Weigelt and Lev-Tov, 2021). This minimally invasive procedure reverses microbial dysbiosis and suppresses tunnel-associated inflammation, thereby reducing the need for excisional surgery (Weigelt and Lev-Tov, 2021). The future development of effective therapeutics targeting tunnels and reducing the need for radical surgical intervention are of the utmost importance in the clinical care of patients with advanced HS. The removal of a tunnel-associated biofilm with minimally invasive flushing in combination with systemic anti-inflammatory therapies could improve outcomes and reduce the need for surgery for moderate and severe HS. Furthermore, understanding the roles and interplay of specific fibroblast populations, keratinocytes, and immune cells in tunnel formation and persistence is required to prevent disease progression and recurrence.

CONCLUSIONS AND FUTURE DIRECTIONS

Elucidation of HS tunnel formation and pathogenesis remains to be a challenge in the field owing to multiple factors. HS has a heterogeneous morphology with various contemporary clinical manifestations, such as nodules, abscesses, and tunnels, all of which may drive diverse gene expression signatures due to distinct cellular compositions (Frew et al, 2018; Gill et al, 2014; Sampath et al, 2025; Saunte and Jemec, 2017). Although single-cell RNA-sequencing data are crucial for identifying the deregulation of major inflammatory pathways and therapeutic targets, only very recent studies have focused on deciphering tunnel pathology using spatial-omics approaches (Adawi et al, 2025). Although the initial studies focused on spatial transcriptomics of early-stage HS (Suh-Yun Joh et al, 2023), further understanding of HS pathogenesis utilizing spatial-omics approaches at different stages of disease progression should be provided to identify pathways involved in tunnel formation and progression. The comprehensive integration of omics data with the system data, including medical electronic records, can lead to a better appreciation for the complexity of underlying factors to enable development of novel therapies targeting HS tunnels and preventing progression of this debilitating disease. These include variables such as the associated microbiota, delayed diagnosis, sex, race, ethnicity, other medical conditions, comorbidities, and medications, all of which affect the pathophysiology of HS. Despite the recognized impact of microbial dysbiosis, current antibiotic-free treatment strategies do not target bacteria in HS tunnels. Because anti-inflammatory therapies are becoming widely used and recognized for modulating dysbiosis in other dermatological

conditions (Callewaert et al, 2020), future studies should evaluate microbiome changes in patients with HS undergoing biological therapy.

Another challenge in understanding the pathogenesis involves the lack of reliable disease models and suitable animal models. The currently used ex vivo HS model uses lesional tissue (Zouboulis et al, 2023) and does not use or resemble HS tunnels, whereas animal models fail to mimic the complexity of HS. Advances in organoid and organotypic skin models utilizing patient cells (Quílez et al, 2024) could provide a basis for preclinical testing of HS in general, including tunnels, with improved translational power.

In conclusion, HS tunnels, which were once regarded as inert structures, have emerged as major contributors to HS pathogenesis. These subcutaneous structures exhibit a multifaceted interplay involving keratinocyte and fibroblast dysregulation; inflammatory processes driven by tunnel keratinocytes, fibroblasts, immune cells, and cytokines; and microbial dysbiosis, presenting significant challenges for successful treatment strategies. HS tunnels are resistant to the currently available treatment modalities, including systemic therapies and antimicrobials, leading to a profound physical, emotional, and economic burden on patients and the healthcare system. Recognizing the HS tunnel resistance to conventional treatments, we propose a compelling argument for early and aggressive interventions to prevent tunnel formation. Although mechanistic studies and improved models are essential to understand tunnel formation, the lack of suitable models that accurately replicate the disease, particularly the formation of tunnels, remains a major challenge. Future research must focus on unraveling the inherent heterogeneity among tunnels, exploring their unique characteristics, and developing novel therapeutically targeted interventions that consider their distinct pathogenic mechanisms.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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