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Unlocking the Mechanisms of Hidradenitis Suppurativa: Inflammation and miRNA Insights

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Abstract: Inflammatory skin diseases impose a significant burden on patients and healthcare systems worldwide. Among these, hidradenitis suppurativa (HS) is particularly notable for its chronic and recurrent nature. Recurrent nodules, abscesses, and scarring in apocrine gland-rich areas characterize the disease, including the groin, axillae, and perianal regions. Despite its considerable physical and psychological impact, the precise mechanisms driving HS remain elusive. Recent advancements in understanding the inflammatory processes involved in HS have highlighted the TNF-alpha, IL-1β, and IL-17/IL-23 pathways, which play crucial roles in initiating and perpetuating the disease. Moreover, specific microRNAs (miRNAs), such as miR-24-1-5p, miR146a-5p, mirR-26a-5p, miR-206, miR-338-3p, and miR-338-5p, are involved in these inflammatory processes. Dysregulation of these miRNAs contributes to aberrant cytokine expression and persistent inflammation, foreseeably exacerbating HS disease progression. This narrative review hypothesizes that miRNA dysregulation triggers aberrant expression in specific inflammatory pathways, contributing to HS's clinical manifestations and progression. We explore the implicated miRNAs' potential as biomarkers for earlier disease detection and as novel therapeutic targets. Identifying miRNA dysregulation offers new opportunities for earlier and more accurate diagnosis, potentially allowing clinicians to intervene before severe disease manifestations occur. Furthermore, therapeutic strategies to modulate miRNA expression could target the inflammatory pathways driving HS, leading to more personalized and effective treatments. This review also discusses future research directions to enhance the clinical management of HS. A better understanding of miRNA involvement in HS offers new avenues for research and management, ultimately improving patient outcomes and quality of life.

Keywords: chronic inflammation, sebaceous glands, inflammatory pathways, immunosuppressant drugs, miRNA dysregulation

Introduction

The Complex Dynamics of HS: Incidence, Influences, and Implications

Painful nodules, abscesses, and sinus tracts characterize hidradenitis suppurativa (HS), a chronic inflammatory skin condition. Historically known by various names such as Velpeau's disease, Verneuil's disease, and acne inversa, HS has long presented a diagnostic and therapeutic challenge due to its complex and multifaceted nature. This debilitating disorder first entered the medical literature in 1839, and the surgeon Verneuil later recognized it as a disorder of the sweat glands in 1854.[1] HS primarily affects the apocrine glands rather than the eccrine sweat glands.[1]

HS clinically manifests through painful, recurrent nodules, abscesses, and extensive scarring, primarily in areas abundant with apocrine glands, including the groin, scrotum, vulva, buttocks, perineum, axillae, intermammary folds, and submammary folds.[2] Despite growing research, the exact prevalence of HS remains uncertain, with estimates ranging from 0.0003% to 4% of the population. The prevalence varies significantly depending on the study population due to the lack of extensive, generalizable prevalence studies.[3] This wide range in predicted disease burden is likely secondary to varying levels of underdiagnosis, patient reluctance to seek treatment, and barriers to patients seeking healthcare between the regions studied.[3,4] More comprehensive epidemiologic studies are necessary to establish a more accurate point prevalence of HS in the United States and internationally.

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Inflammation plays a central role in both the initiation and progression of HS, suggesting that managing inflammation is pivotal for effective treatment. This narrative review critically investigates the intricate inflammatory processes underpinning HS, explicitly focusing on critical pathways, including TNF-alpha, IL-1β, and IL-17/IL-23. Recent studies highlight miRNA dysregulation in these pathways that may trigger and exacerbate the characteristic symptoms of HS. Significant differences in circulating miRNA expression, including miR-24-1-5p, miR-146a-5p, miR26a-5p, miR-206, miR338-3p, and miR-338-5p, exist between HS patients and healthy controls, highlighting their potential as biomarkers for earlier disease detection.[5] Emerging research suggests a genetic component in the development of HS, as many patients report a family history of the disease.[6] Genetic mutations, especially those involving the γ-secretase complex, contribute to familial cases, indicating a hereditary role in HS pathogenesis.[7] Additionally, genetic studies have demonstrated associations between HS and other autoinflammatory diseases, reinforcing the significance of genetics in disease progression.[7] This review identifies both consistencies and discrepancies in the current understanding of HS. Exploring how both genetic and inflammatory mechanisms contribute to the disease's clinical features and progression sheds light on the fundamental mechanisms of HS and discusses the potential of emerging therapies that target these specific inflammatory mediators.

This review aims to provide a detailed understanding of the inflammatory basis of HS and highlight the importance of targeted therapeutic strategies that potentially transform clinical management. We focus on modulating inflammatory components and setting the stage for future research directions, promising advancements in treatment options, and improved outcomes for patients suffering from this debilitating condition.

Decoding Genetic and Environmental Triggers in Hidradenitis Suppurativa

Risk factors for HS include a combination of environmental and genetic factors. Research suggests that 34% of HS patients have a first-degree relative affected by the condition.[6] Several genetic markers associated with HS have been identified, including variations in genes involved in inflammatory pathways. Notably, mutations in the γ-secretase gene have been linked to a subset of familial cases, implicating this gene in the disease's pathogenesis.[7] Additional studies are needed to establish the heritability of HS further.

In addition to genetic factors, lifestyle choices significantly impact the development and severity of HS. Factors such as smoking and obesity are well-documented risk factors that exacerbate the condition. A vast majority of HS patients (70–89%) are known tobacco users, suggesting a strong association between tobacco use and HS outbreaks.[6] This association is attributed to tobacco's effect on sweat glands' function and neutrophil chemotaxis alteration.[8] Obesity is another significant risk factor, with studies indicating that up to 50% of HS patients are also obese. Obesity increases sweat retention, skin friction, pore occlusion, androgen excess, as well as altered immune responses, which may exacerbate the skin inflammation characteristic of HS.[6,9,10]

HS affects women at a ratio of approximately 3:1 compared to men in Europe and North America, while in Asian populations, HS affects men at 2:1 compared to women.[11,12] These unique trends in HS incidence have been partially attributed to the tobacco smoking habits in each area, with Europe and North America having a more significant proportion of female to male smokers. In comparison, Asian countries tend to have a higher proportion of male tobacco smokers.[11,12] Gender also impacts HS presentation, with females having more frequent lesions in the breast and groin areas and men having more gluteal involvement.[12] Lastly, the male gender has been associated with increased severity of lesions when classified using Hurley stages.[12] These trends suggest that hormonal and behavioral differences between males and females influence the gender differences in HS. The relationship between gender and HS is not yet fully understood, and more studies are needed to establish the impact of gender on HS onset and presentation.

These environmental factors, in conjunction with genetic predispositions, play crucial roles in the development and progression of HS, highlighting the need for a multifaceted approach in both research and treatment of this challenging condition. The interplay between genetic predisposition and environmental triggers for HS remains under-researched. Additional studies are needed to explore the mechanistic pathways through which environmental factors exacerbate genetic vulnerabilities in HS.

Characterizing Clinical Presentation and Phenotypes in Hidradenitis Suppurativa

HS causes painful, inflamed nodules and abscesses in areas of the body rich in apocrine glands, such as the axillae, groin, and perianal regions. The clinical presentation of HS can vary significantly but generally begins with pimple-like bumps that progress over time to form deeper abscesses. As the disease advances, these lesions can develop into sinus tracts and extensive scarring, which are hallmark features of the condition.[13]

Patients with HS may experience severe pain and frequent flare-ups, which significantly impair their quality of life. The lesions often lead to pus formation and malodorous discharge, adding to the discomfort and social stigma associated with the disease. Repeated inflammation over time leads to scarring and fibrosis. This can limit movement depending on the areas involved.[13]

The clinical course of HS typically includes periods of flare-ups followed by remission. During flare-ups, the nodules and abscesses become particularly inflamed and painful. The chronic and relapsing nature of HS makes management challenging and often requires a combination of treatment strategies to control symptoms and prevent progression.[13] Notable variations exist in the presentation of HS, with patients predominantly experiencing either a follicular or inflammatory phenotype. Nodules and comedones characterize the follicular subtype, while the inflammatory subtype is more aggressive, featuring frequent abscesses and extensive, often interconnected, scarring. These phenotypic distinctions are essential for guiding treatment decisions and understanding the potential progression of the disease in individual patients.[14]

Diagnostic Criteria and Assessment Strategies for Hidradenitis Suppurativa

Hidradenitis suppurativa is a complex and often misdiagnosed condition that requires a specific set of criteria for accurate diagnosis. According to established clinical guidelines, three diagnostic criteria are pivotal: (1) specific lesion morphology, including features such as single or double open comedones, papules, nodules, abscesses, sinus tracts, fistulas, and scarring; (2) characteristic distribution of lesions, typically in the axillary, inframammary, groin, perineal, and gluteal regions; and (3) chronicity and recurrence, with the patient experiencing more than two lesions for at least six months.[15] Meeting these criteria allows for a diagnosis with 90% sensitivity and 97% specificity, emphasizing the importance of precise clinical assessment.[15]

HS has an average diagnostic delay of 7.2 years compared to 1.6 years in psoriasis patients, showing the need for better diagnostic criteria and more awareness among healthcare providers.[16] This discrepancy highlights the more significant challenge in diagnosing HS compared to psoriasis, despite both conditions being chronic inflammatory diseases with substantial patient impact. Additionally, longer diagnostic delays are associated with a family history of HS, potentially because of higher thresholds for seeking medical assistance, familial normalization of symptoms, and general practitioners who misdiagnose may not recognize the genetic links and typical presentations of the disease.[17]

The physical examination of a patient suspected of having hidradenitis suppurativa might reveal inflamed and non-inflamed nodules and draining and non-draining sinus tracts, primarily in the axillae, groin, and anogenital areas. These findings are crucial for differentiating HS from other dermatological conditions, such as simple boils, often misdiagnosed as HS. HS lesions are rounded and deeper in the dermis, distinguishing them from the pointed, purulent appearance typical of boils. In unclear or resistant cases, further diagnostic measures such as biopsies, bacterial cultures, and ultrasonography may be necessary to confirm the diagnosis and plan appropriate treatment strategies.[18,19]

The Hurley staging system is a widely used, reliable clinical framework that assesses HS severity and categorizes the disease into three stages based on the presence and extent of abscesses, sinus tracts, and scarring (Table 1).[20] Clinicians commonly use this staging to guide treatment decisions and evaluate the disease's impact on quality of life. Each stage progressively affects patients more severely, not just physically but also emotionally and socially, highlighting the importance of appropriate and timely treatment interventions. Despite the usefulness of the Hurley system, a critical need exists for more sensitive and specific diagnostic tools to identify HS earlier in its course. The diagnosis is often delayed, with patients typically visiting a physician at least five times before receiving a diagnosis and experiencing an average

Table 1 Hurley Staging Classification

Hurley Stage	Description
1	Isolated abscesses without any sinus tracts or scarring.
2	The separation of normal skin areas with recurrent abscesses, which have one or more sinus tracts and scarring.
3	Diffuse involvement with multiple interconnected sinus tracts and abscesses and no intervening skin.

delay of 10 years.[21] Visiting a dermatologist increases the likelihood of initiating treatment for HS and escalating therapy.[22]

Ultrasonography is a valuable tool for identifying subclinical HS that may not be apparent during routine clinical examinations.[14] Using ultrasound in routine diagnostics can help diagnose HS faster. This allows for earlier treatment and intervention at the initial stages of the disease. Moreover, using ultrasound alongside physical examination findings enhances the accuracy and consistency of HS staging. This improved diagnostic approach allows for more appropriate treatment recommendations and facilitates better comparison of treatment responses.[23] Developing a point-of-care diagnostic aid for non-dermatologists to identify HS features accurately is advantageous. Such an initiative would facilitate rapid diagnosis and timely initiation of care, ultimately improving patient outcomes and reducing the disease burden.[22] In addition to imaging techniques, molecular biomarkers provide another promising diagnostic tool. Identifying circulating miRNAs as potential biomarkers offers a promising avenue for early diagnosis. Significant differences in miRNA expression profiles, such as miR-338-5p, have been observed in HS patients, indicating their potential role in early disease detection and monitoring.[5]

Epidermal wearable biosensors offer a promising tool for early detection and continuous monitoring of HS inflammatory markers and miRNA levels. These non-invasive, flexible devices have successfully monitored biomarkers for chronic diseases like diabetes and cystic fibrosis, offering real-time data through sweat analysis.[24] Wearable biosensors enable continuous glucose monitoring in diabetes, allowing timely interventions and improving patient outcomes. Similarly, these sensors measure chloride levels in sweat for cystic fibrosis, aiding in early diagnosis and management.[25] These devices revolutionize chronic disease management by providing consistent, real-time data that allows for precise tracking of disease progression and treatment effectiveness. For HS patients, integrating this technology could monitor inflammatory markers such as TNF-α, IL-1β, and IL-17, which are crucial in the disease's pathogenesis. Monitoring these markers would help understand real-time inflammatory processes and evaluate treatment efficacy. Monitoring miRNAs like miR-223, miR-146a-5p, miR-155, and miR-338-5p could offer insights into miRNA dysregulation, providing potential biomarkers for early detection and disease progression. However, challenges such as the need for high sensitivity, stability, and selectivity in wearable sensors and the importance of validating these sensors through longitudinal and cross-sectional studies remain.[26] Developing next-generation sensors that can monitor a broader spectrum of biomarkers is crucial for future research.

In addition to the technological advancements in wearable biosensors, the impact of epigenetic changes on gene expression in HS is also emerging as a significant area of study. Epigenetic modifications, such as DNA methylation and histone modifications, significantly alter the expression patterns of miRNA genes in HS patients compared to healthy controls. Sixty identified CpG sites involving 65 miRNA genes with significant methylation differences occur between HS cases and controls, indicating the crucial role of these epigenetic changes in HS pathogenesis.[27] Specific miRNAs, such as miR-29, miR-200, miR-205, miR-548, and miR-132, are critical for skin function and repair and are epigenetically altered in HS.[27] For instance, miR-200c regulates skin repair after injury, while miR-132 is upregulated during inflammation, promoting keratinocyte proliferation.[27,28] Pathway analyses have highlighted key biological pathways active in HS, such as Wnt signaling, responsible for regulation of cell growth and development, and cytokine-mediated pathways inflammatory pathways involved in inflammation. Targeting these pathways with specific treatments could lead to new therapeutic strategies for managing HS.[29]

Evolution of Hidradenitis Suppurativa Treatment Strategies

Treating HS is challenging for physicians, as there is no single best management option. Historically, clinicians treated HS with antibiotics, steroids, phototherapy, and surgery. However, managing hidradenitis suppurativa has evolved significantly in recent years due to the introduction of advanced biological therapies and more personalized treatment strategies. Given the inflammatory nature of the disease, emerging research has been exploring medications that target specific inflammatory markers known to contribute to the pathogenesis of the condition, such as TNF-α, interleukin-17 (IL-17), and Janus kinase (JAK) pathways. While generally safe, these immunomodulators may rarely increase the risk of infections and malignancies due to long-term immune system suppression.[30]

Adalimumab, a monoclonal antibody for TNF-α, is the first FDA-approved biologic for HS and other inflammatory skin conditions. Randomized control trials show that it reduces the overall number of inflammatory nodules and abscesses by up to 50% in moderate to severe cases.[31,32] A reduction in over half of a patient's lesions can significantly impact a patient's quality of life and pain. However, Adalimumab does not give patients complete resolution of lesions, highlighting the need for further research into potentially curative treatments.[33]

In addition to TNF-α inhibitors, newer biologics targeting IL-17, such as secukinumab, have emerged. Secukinumab directly targets the inflammatory pathways that drive HS and shows promise in clinical trials, reducing its severity. Patients often report improvements in pain and reduced size and number of skin lesions.[34]

JAK inhibitors, such as tofacitinib and ruxolitinib, target the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, a key regulator of immune responses and inflammation in HS, making them promising treatment options.[35] Early clinical trials suggest these agents may reduce the severity, modulating immune cell activity and cytokine production, thus offering a new avenue for therapy-resistant HS.[36]

The treatment regimen for HS may also include other pharmaceutical options, such as antibiotics, which take advantage of their antibacterial properties and ability to reduce inflammation. These therapies typically involve clindamycin and rifampicin, administered for several months to manage the bacterial load and inflammation commonly associated with HS. Hormonal treatments, including antiandrogens like spironolactone, have been beneficial in some patients, particularly in managing flares related to menstrual cycles in women.[37]

For patients who do not respond to pharmaceutical treatments or who suffer from severe and persistent lesions, surgical interventions may be necessary. Deroofing, which involves removing the roof of sinus tracts or abscesses, can provide relief and reduce lesion recurrence. In more severe cases, wide excision, which involves removing extensive areas of affected skin, may be recommended.[38,39] These surgical options, including the emerging use of CO_2 laser for less invasive management, require careful planning and follow-up to manage healing and prevent complications. The surgical approach often depends on the disease's severity and the specific areas affected, focusing on removing all affected tissue to minimize recurrence.

New techniques have explored the role of laser therapy and photodynamic therapy in managing HS. These modalities provide alternatives for patients who are either not candidates for surgical interventions or have not responded adequately to pharmacological treatments. Studies report success in reducing lesion size and pain, mainly using Neodymium-doped Yttrium Aluminum Garnet lasers. These lasers target inflamed hair follicles and reduce bacterial load, diminishing inflammation and improving symptoms.[40]

Lifestyle modifications play a crucial role in managing HS. Recommendations often include weight management, smoking cessation, and careful skin care to prevent the development of new lesions and to manage existing symptoms. The Western diet, particularly dairy and refined carbohydrates, also plays a role.[41,42] Dairy components such as casein, whey, and androgens, along with insulin and IGF-1 from simple carbohydrates, contribute to follicular occlusion and inflammation.[43] Dietary modifications decrease inflammation and aid in weight loss, improving obesity-related issues such as reducing friction in skin folds.[41] While most evidence points to these food groups, other studies suggest addressing micronutrient deficiencies such as zinc and vitamin D, adopting a ketogenic diet, or eliminating wheat and brewer's yeast in specific populations.[41,42,44] Challenges in conducting controlled dietary trials and the absence of robust clinical trials result in weak clinical recommendations.[42] Studies examining the gut microbiome in patients with HS are limited; however, one small study revealed an alteration in the gut microbiome compared to controls.[45] These deficits

highlight an opportunity for further research to improve the management of HS via dietary interventions and optimizing the gut-skin-brain axis.

Overall, the management of HS is moving towards more tailored and multi-modal approaches, incorporating both established and novel therapies. This integrated approach aims to manage symptoms and address the underlying causes of HS, thereby improving patients' overall quality of life. Exploring miRNA mimics or inhibitors could provide a new way to modulate inflammatory pathways in HS, improving treatment outcomes. As research unveils new aspects of HS pathophysiology, treatment paradigms will evolve, offering hope for more effective and sustainable management strategies.

Comprehensive Impact of HS: Physical, Systemic, and Psychological Challenges

Hidradenitis suppurativa presents a diverse range of physical challenges, both cutaneous and systemic, profoundly impacting the quality of life of HS patients. Cutaneous manifestations include the formation of sinus tracts, fistulae, scarring, and contractures, which not only cause discomfort but also an increased risk for skin cancer development.[46] A heightened incidence of keratinocyte carcinoma and a correlation occurs between HS and squamous cell carcinoma, particularly in the perineal and gluteal areas. This finding is likely due to the chronic inflammation in these regions exposed to bacterial, fungal, and viral infections, leading to proliferative changes conducive to neoplastic development.[47] The incidence of skin cancer in HS patients is 1,656 per 100,000 patients, with keratinocyte carcinoma making up 1,476 of the cases.[47] Moreover, a study in Korea found that patients with HS also have increased risks for Hodgkin lymphoma, pharyngeal and oral cavity cancer, central nervous system cancers, prostate cancer, and colorectal cancer.[48] Systemically, HS can lead to chronic pain, systemic amyloidosis, and anemia.[49] HS has a significant psychosocial impact, leading to poor body image and mental health challenges.[7] There is also an increased risk of cardiovascular events and mortality in HS patients, likely due to chronic inflammation and elevated levels of C-reactive protein and TNF.[50] Despite extensive research identifying a wide array of complications, significant gaps remain in a better understanding of the long-term complications of HS. More extensive, longitudinal studies are necessary to evaluate this wide array of long-term effects complicating various organ systems. Understanding these impacts is crucial for developing comprehensive management strategies that address HS patients' immediate and future health concerns.

Going beyond the physical, living with HS inflicts a profound toll on mental health and well-being. Patients report feelings of stigma, diminished body image, and negative impacts on sexual health, leading to disruptions in intimate relationships.[51,52] These challenges extend into the workplace, with 50–58% of HS patients reporting absenteeism and a high unemployment rate compared to the general population.[53] Severe chronic pain affects 97% of HS patients, often leading to insomnia, diminished sleep quality, and daytime dysfunction.[54] In addition, an elevated risk of suicide is a concern. With depression affecting 42.9% of HS patients, there is an increased use of antidepressants and anxiolytics, and a higher rate of mental health-related hospitalizations.[55] While substantial data indicate HS's severe psychological and social impacts, further research and development of more effective interventions are essential in improving these patients' overall quality of life.

Molecular and Immunological Insights into Hidradenitis Suppurativa Pathogenesis

The pathogenesis of hidradenitis suppurativa involves complex and multifactorial processes. A key event in HS is the occlusion of follicles within the follicular pilosebaceous unit, leading to recurrent, painful nodules and abscesses.[56] The initial occlusion event is pivotal, leading to follicular rupture, inflammation, and lesion formation, which are central phenomena in the pathophysiology of HS.[57] The subsequent rupture of these occluded follicles discharges keratin and other cellular materials into the surrounding dermis. The release of pro-inflammatory cytokines, such as IL-1β and tumor necrosis factor-alpha (TNF-α) provokes a robust immune response with the involvement of mediators from Th1 and Th17 cells, including interferon-gamma (IFN-γ) and IL-17. Further, the activation and recruitment of neutrophilic granulocytes, macrophages, and plasma cells contribute significantly to the chronic inflammation and tissue damage

characteristic of HS.[9] This complex interplay between innate and adaptive immunity components highlights the intricacy of HS's pathogenic mechanisms.[9] However, the initial triggers of follicular occlusion are still poorly understood, necessitating detailed molecular studies to map these early events. Understanding these triggers is crucial for developing preventive strategies or targeted therapies to modulate the subsequent inflammatory responses.[9]

Although follicular occlusion is known to trigger HS, the exact initiating factors remain poorly understood. Evidence suggests a multifactorial etiology, where genetic predispositions, hormonal imbalances, and environmental factors converge to disrupt normal follicular keratinization processes.[9] Interestingly, variability occurs in the findings related to genetic factors. For example, while Nomura (2020) highlights the role of γ-secretase mutations in HS pathogenesis, Orobets & Karamyshev (2023) suggest that these mutations alone may not be sufficient to trigger the disease without specific environmental triggers or co-existing genetic abnormalities.[58,59] This discrepancy underscores the complexity of genetic influences in HS. The disease process in HS begins with the occlusion of hair follicles, which triggers a chain of inflammatory responses involving a wide array of cytokines and immune cells.[57] Following the initial occlusion of hair follicles in HS, complex biochemical processes lead to inflammation, nodules, abscesses, and sinus tract formation.[60]

HS is currently divided into familial, sporadic, and syndromic forms to understand the genetic influences further. In the familial form, more than one-third of patients with HS report a family history of the disease, which may follow an autosomal dominant inheritance pattern with incomplete penetrance.[61] Genetic factors that contribute to HS's pathogenesis include mutations in genes encoding γ-secretase components (*NCSTN, PSENEN, and PSEN1*). These mutations result in dysregulated hair follicle differentiation, hyperkeratosis, and cyst formation due to aberrant Notch signaling, further complicating the disease mechanism.[58] Recent studies, however, present varying results regarding the prevalence and impact of these mutations. For instance, Orobets & Karamyshev (2023) extended Nomura's work,[58] relying heavily on familial case studies. They analyzed familial and sporadic cases, uncovering a broader spectrum of genetic variations.[58,59] Their study suggests that while γ-secretase mutations are prevalent in many HS cases, their pathogenic impact might differ based on additional genetic and environmental factors not fully explored in earlier studies.

These genes are also implicated in Alzheimer's disease (AD), where their gene products process the amyloid precursor protein (APP) and contribute to amyloid-β production.[59] However, in HS, their role is more aligned with regulating follicular differentiation and inflammation, highlighting the distinct pathogenic mechanisms despite the shared genetic factors.[62] Despite these insights, longitudinal studies do not link genetic predispositions with long-term disease outcomes. Such studies are crucial as they could help clarify the role of genetics in HS progression and treatment response. Longitudinal research could provide valuable data on how genetic factors interact with environmental and hormonal influences over time, offering a more comprehensive understanding of HS pathogenesis and informing more effective, personalized treatment strategies.

Patients with HS may have an increased risk of developing Alzheimer's disease due to the γ-secretase complex mutations. Unlike the Orobets & Karamyshev[59] analysis, other studies show a connection between these mutations and familial HS and Alzheimer's disease.[59] Altered Notch signaling drives the Inactivation of γ-secretase in mouse skin and causes histologic abnormalities similar to HS.[63] A Danish cohort study found that the incidence rates of Alzheimer's disease were 3.81 per 10,000 person-years for HS patients compared to 2.64 for the control population. The study reported an adjusted hazard ratio of 1.44, indicating a slightly elevated risk, but concluded that the results were not statistically significant, indicating no increased risk of AD among HS patients.[64] A study in Turkey showed a higher prevalence of AD in HS patients with a family history of HS, indicating a 4.5 times greater risk, increasing to 8.8 times in individuals over 40.[65] However, this study noted that the results were not statistically significant due to limitations such as low sample size and lack of genetic confirmation of AD diagnoses. A US study found HS linked to a higher AD risk (OR: 1.23), suggesting HS as a potential AD risk factor, but found no statistically significant increased risk of AD after adjusting for age and sex.[64] Additionally, the US study could not isolate the HS cohort to the subset of familial patients with the genetic mutations implicated in both HS and AD.[64]

This variability in findings underscores the need for further studies that focus on broader genetic screening and incorporate environmental assessments to understand better the interactions that lead to HS in the presence of γ-secretase mutations. Comparing these divergent outcomes also raises questions about the genetic heterogeneity of HS and the potential for distinct pathogenic pathways even within genetically predisposed individuals. The variability in findings

across different populations and study designs may be because the two diseases show significant differences in peak times and most destructive periods. HS often appears in the third decade of life, whereas AD typically manifests at a later age, usually over 40 years.[66] Therefore, retrospective analysis without a lifetime follow-up may overlook a possible association between the two diseases.

HS-related immunological reactions may also contribute to AD. Elevated Th17 cells and interleukin levels in AD patients suggest a role in its pathogenesis, and treatments targeting these pathways have shown promise in reducing neuroinflammation and improving memory.[67] This connection highlights the importance of understanding the shared immune mechanisms in HS and AD, as targeting Th17 cells and IL-17A could offer a novel therapeutic approach for managing HS's inflammatory aspects and potentially mitigating neurodegenerative processes in AD. Further research into these shared pathways could lead to more effective treatments for both conditions. Exploring these immune mechanisms provides valuable insights into the shared pathways between HS and AD and the broader implications of immune dysregulation in chronic inflammatory diseases.

The success of biologics in treating HS supports the idea that aberrant immunity, rather than bacterial infection, plays a significant role in its pathogenesis. Biologics targeting TNF-α, such as infliximab and Adalimumab, have shown considerable efficacy in reducing inflammation and improving clinical outcomes, highlighting the pivotal role of immune dysregulation in HS pathogenesis.[29,61] However, variability occurs in patient response to TNF-α inhibitors. Some studies report limited or no response in specific patient populations, which may be due to genetic factors, environmental influences, or the severity of the disease.[68] Increased levels of TNF-α, IL-17, IL-1, and C5a have been detected in the lesional tissue of HS patients, supporting the rationale for selectively targeting these inflammatory pathways.[69] TNF-α is a nonspecific inflammatory cytokine with inferior clearance and response rates compared to IL-17 and IL-23 inhibitors in psoriasis.[70] This is particularly relevant for HS, as both conditions share similar inflammatory pathways and cytokine profiles, suggesting that insights from psoriasis treatment can inform HS therapy optimization. Understanding these discrepancies is crucial for optimizing treatment strategies.

Other biologics targeting IL-17, such as secukinumab, and IL-1 inhibitors like anakinra, have also demonstrated effectiveness, further supporting the immunological basis of the disease.[71] IL-17 inhibition is promising due to Th17 cells in HS lesions and evidence of IL-17 blockade efficacy. Strong IL-17 signals are seen in moderate and severe disease, suggesting IL-17 may be beneficial where TNF-α therapy has failed.[72] However, IL-17 antagonism may worsen inflammatory bowel disease (IBD), often associated with HS.[73] Genetic studies have identified the absence of a minor allele (TNF-like ligand 1A) linked to non-response in these patients.[74] Therefore, pharmacogenomic indicators might predict benefits in patients with HS and IBD. The observed variability in treatment response could be due to different disease phenotypes or underlying genetic factors, highlighting the need for personalized treatment approaches.

Understanding the complexity of HS's disease mechanisms is essential, as current research converges on three key pathways: TNF-α, IL-1β, and the IL-17/IL-23 axis, which are crucial in driving the inflammatory processes underlying HS. Understanding these pathways further elucidates the mechanisms behind these therapeutic strategies, highlighting their critical involvement in HS pathology.

Decoding the TNF-α Pathway: Its Role in Inflammation and Tissue Damage in HS

In HS, the initial pathological event involves follicular occlusion, which culminates in the rupture of dilated follicles, releasing keratin fibers, commensal flora, and pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) into the dermis.[75] This dispersal activates macrophages via Toll-like receptors (TLRs) and the NLRP3 inflammasome, prompting the secretion of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines stimulate fibroblasts and keratinocytes to produce chemokines like CXCL1, CXCL6, CXCL8, and CCL20, which recruit various inflammatory cells, leading to the development of nodules, abscesses, and fistulas.[76] Additionally, TNF-α exacerbates the inflammatory response and skews the Th17/Treg cell balance, resulting in increased Th17 cell production and subsequent recruitment of neutrophils, T cells, and monocytes to the skin.[77]

The TNF-α pathway primarily operates through two receptors, TNFR1 and TNFR2. TNFR1, also termed CD120a or p55, predominantly orchestrates pro-inflammatory and apoptotic responses via activation of intracellular signaling cascades involving NF-κB and MAPK pathways critical for immune responses and cell death.[78] Upon TNF- α binding,

TNFR1 triggers the NF-κB and MAPK signaling pathways and recruits adaptor proteins like TRADD and RIP1, activating IKK and subsequent degradation of IκB. This process releases NF-κB, which translocates into the nucleus to stimulate inflammatory gene expression. Concurrently, TNFR1 activation can stimulate MAPK pathways (ERK, JNK, p38), which regulate gene expression and apoptosis, with the JNK pathway particularly associated with pro-apoptotic activities under specific conditions.[79]

Conversely, TNFR2 (CD120b or p75) primarily supports tissue regeneration and immune modulation, lacking a death domain and predominantly activating pathways promoting cell survival and proliferation.[78] Its involvement extends to enhancing cellular responses during tissue repair and regeneration, highlighting its role in both protective and potentially pathological processes in chronic inflammatory conditions such as HS.

In HS, TNFR1 predominantly mediates the inflammatory effects associated with TNF- α signaling. A marked increase in TNF-α-regulated gene expression within HS lesional skin highlights TNFR1's critical role in orchestrating inflammatory responses. The significant involvement of TNFR1 underscores its value as a therapeutic target. Clinicians have effectively utilized specific TNF- α inhibitors, such as infliximab and Adalimumab, to inhibit this pathway, reducing inflammation and improving overall outcomes for HS patients.[68]

IL-1β Pathway's Contribution to Chronic Inflammation and Lesion Formation in HS

Macrophages primarily secrete IL-1β, initiating and propagating the inflammatory response, leading to the characteristic lesions observed in HS.[58] The IL-1 pathway is particularly noteworthy because the release of follicular content activates the NLRP3 inflammasome, a critical mediator of IL-1 family cytokine production.[77] The pro-inflammatory cytokine IL-1β binds to its cognate cell surface receptor, IL-1R1, and initiates IL-1β signaling. This binding facilitates the recruitment of the IL-1 receptor accessory protein (IL-1RAcP), forming a heterotrimeric complex that triggers the intracellular signaling cascade. The adaptor protein MyD88 (myeloid differentiation primary response 88) is then recruited to the receptor complex, leading to the subsequent assembly of the IRAK (IL-1 receptor-associated kinase) family and TRAF6 (TNF receptor-associated factor 6). This assembly activates TAK1 (TGF-β activated kinase 1), a critical kinase that further propagates the signal through two major pathways: the NF-κB and MAPK pathways.[80] Activation of NF-κB and MAPK pathways results in the transcription of several pro-inflammatory genes, amplifying the inflammatory response essential in the context of HS. This detailed pathway underscores the potent inflammatory role of IL-1β, driving the persistent inflammation observed in HS.

Critical Functions of the IL-17/IL-23 Axis in Driving HS Pathogenesis

The IL-17/IL-23 axis plays a vital role in the immune system, especially in inflammatory conditions like HS. Dendritic cells and macrophages produce IL-23 and initiate this axis, which involves several key steps. IL-23 is crucial for activating and expanding Th17 cells, a subtype of T-helper cells that produce IL-17, a cytokine integral to inflammatory responses.[81]

Th17 cells secrete IL-17 upon activation, which binds to IL-17 receptors on various target cells, including epithelial and endothelial cells, fibroblasts, and macrophages. This binding triggers intracellular signaling pathways, such as the activation of NF-κB and MAPK, leading to the transcription of genes that encode several other inflammatory mediators. These mediators include cytokines like TNF-α, IL-6, and chemokines, which further recruit and activate more immune cells, perpetuating the inflammatory cycle.[69,81]

In HS, the chronic activation of this pathway results in persistent inflammation, which is seen as nodules, abscesses, and extensive scarring. The IL-17/IL-23 axis drives these pathological changes and underlines the therapeutic potential of targeting this axis. Inhibiting components of this pathway, particularly IL-17 or IL-23, offers a promising approach to mitigate inflammation and improve clinical outcomes in HS patients, demonstrating the axis's pivotal role in the pathogenesis and management of the disease.

Impact of microRNA Dysregulation on HS Pathophysiology

MicroRNAs (miRNAs) have emerged as regulators in the pathogenesis of hidradenitis suppurativa, specifically influencing key inflammatory mediators within the TNF-α, IL-1β, and IL-17/IL-23 pathways and contributing significantly to

the complex clinical manifestations of the disease.[29] Recent studies have found significant overexpression of miRNA-155-5p, miRNA-223-5p, miRNA-31-5p, miRNA-21-5p, and miRNA-146a-5p in lesional HS skin compared to healthy controls, suggesting their involvement in the inflammatory processes of HS.[82] These miRNAs have regulatory roles in the inflammatory pathway; miRNA-155-5p promotes pro-inflammatory cytokine production, and miRNA-146a-5p is a negative regulator of TNF-α production.[82]

MicroRNAs are post-transcriptional regulators of gene expression, consisting of small, non-coding RNA molecules, approximately 22 nucleotides in length.[5] They bind to complementary sequences on target messenger RNAs (mRNAs), leading to either mRNA degradation or inhibition of translation. This regulatory mechanism controls various biological processes, including cell growth, differentiation, apoptosis, and metabolic regulation. In the context of diseases, miRNAs modulate pathological processes and affect cellular signaling pathways involved in inflammation and immune responses.[29,61,83] miRNAs such as miR-223, miR-146a-5p, miR-155, and miR-338-5p are key regulators of immune and inflammatory responses.[84,85] In HS, specific miRNAs are dysregulated, potentially altering the expression and activity of inflammatory mediators within the TNF-α, IL-1β, and IL-17/IL-23 pathways.[83] De Felice et al (2022) and Moltrasio et al (2024) suggest significant involvement of miRNAs like miR-146a-5p and miR-338-5p.[5,29] The robustness of evidence linking specific miRNAs to HS pathophysiology varies. While the De Felice et al (2022) and Moltrasio et al (2024) studies provide compelling data, whether these miRNAs play a causative role or merely correlate with disease severity remains unclear.[5,29] Alternative interpretations of the data can be considered, and more rigorous experimental designs are needed to establish causation. It remains essential to consider whether other, non-explored miRNAs or molecular mechanisms influence the disease.

The intricate interplay between miRNAs and epigenetic modifications deepens the understanding of HS's molecular underpinnings and highlights potential strategies for targeted therapeutic interventions. As miRNAs such as miR-155 and miR-223 are involved in both the direct regulation of inflammatory pathways and are themselves subject to epigenetic modifications, targeting these pathways offers a promising therapeutic avenue to lead to significant advancements in HS management, ultimately offering more precise and potent treatment modalities (Table 2 and Figure 1).[29,86]

miR-223

miR-223 regulates the differentiation and function of myeloid cells, impacting HS's inflammatory and immune responses. Abnormal expression of miR-223 in HS can alter neutrophil and macrophage activation, leading to an exacerbated inflammatory state. This miRNA specifically affects the signaling pathways that control the production and release of key inflammatory mediators, such as IL-6 and TNF-α, enhancing the recruitment and activation of further immune cells to the inflamed tissue.[29,61] This suggests that targeting miR-223 could lessen inflammation and provide symptomatic relief in HS patients.

Table 2 microRNAs and Their Role in the Pathophysiology of Hidradenitis Suppurativa

miRNA	Regulation	Function in HS	Potential Therapeutic Approach
miR-223	Neutrophil and macrophage activation	Enhances cytokine production, exacerbating an inflammatory state	Targeting miR-223 to reduce inflammation
miR-146a-5p	NF-κB signaling pathway components	Increases TNF-α and IL-6, promoting a pro-inflammatory environment	Modulating miR-146a-5p to attenuate inflammatory responses
miR-155	Cytokine networks involving TNF-α	Disrupts cytokine expression, contributing to chronic inflammation	Using inhibitors to manage cytokine-driven inflammation
miR-338-5p	Cytokine signaling pathways	Associated with increased cytokine production and disease severity	Investigating as a biomarker for disease activity and targeting for reduced cytokine-mediated inflammation

Notes: Adapted from De Felice et al (2022).[29]

Abbreviations: HS, hidradenitis suppurativa; IL, Interleukin; JAK, Janus Kinase; signal transducer and activator of transcription (STAT); TNF, tumor necrosis factor; IFN, interferon; Alzheimer's disease, AD; APP, amyloid precursor protein; IBD, irritable bowel disease; PAMP, pathogen-associated molecular patterns; DAMP, damage-associated molecular patterns; TLR, Toll-like receptor; miRNA, microRNA; RacP, receptor accessory protein; MyD88, myeloid differentiation primary response 88; mRNA, messenger RNA; IRAK, IL-1 receptor-associated kinase; TRAF6, TNF receptor-associated factor 6; TAK1, TGF-β activated kinase 1.

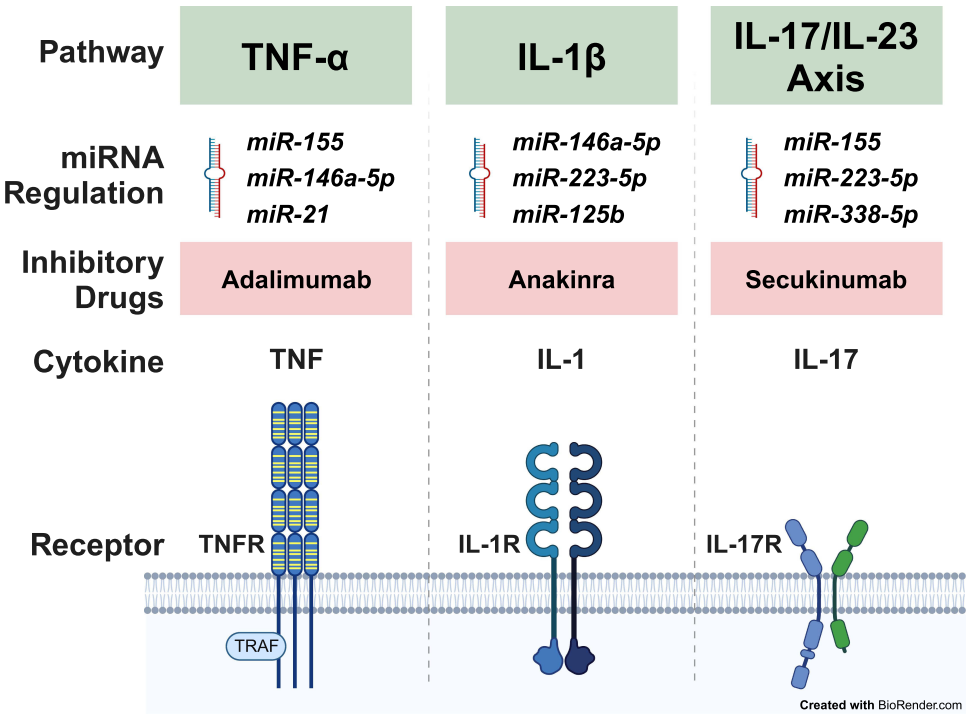

Figure 1 The regulation of key inflammatory pathways implicated in the pathogenesis of hidradenitis suppurativa (HS), emphasizing the roles of specific microRNAs (miRNAs) and the inhibitory drugs used in treatment. The TNF-α, IL-1β, and IL-17/IL-23 pathways are shown with details of their respective miRNA regulators and targeted biologic therapies. In the TNF-α pathway, miR-155 and miR-21 promote, while miR-146a-5p inhibits TNF-α production,[82,87] with Adalimumab as the inhibitory drug targeting TNF-α and reducing inflammation,[33] In the IL-1β pathway, miR-146a-5p[88] and miR-125b inhibit,[89] while decreased miR-223-5p promotes IL-1β production,[90,91] with Anakinra as the IL-1 receptor antagonist that blocks IL-1β activity, alleviating inflammatory symptoms.[80] The IL-17/IL-23 axis involves miR-155, miR-223-5p, and miR-338-5p, promoting IL-17 production,[82,87] with Secukinumab targeting IL-17A to neutralize its activity and reduce inflammation.[32] These pathways interact at the cellular level, where TNF-α binds to TNFR, IL-1β binds to IL-1R, and IL-17 binds to IL-17R, triggering signaling cascades that promote inflammation and keratinocyte proliferation. miRNAs critically regulate these cytokines, modulating inflammation severity. Therapeutic interventions with Adalimumab, Anakinra, and Secukinumab specifically inhibit these pathways, reducing the chronic inflammatory state in HS and alleviating symptoms, reducing lesion formation, and improving patient quality of life. This figure underscores the intricate network of cytokines and miRNAs in HS pathology and highlights targeted biologic therapies' potential benefits in managing this debilitating condition. Created in BioRender. Ames, E. (2024) BioRender.com/b79d837.

miR-146a-5p

miR-146a-5p targets components of the NF-κB signaling pathway, such as IRAK1 and TRAF6, regulating the transcription of inflammatory cytokines. In HS, upregulation of miR-146a-5p leads to increased NF-κB activity, promoting a pro-inflammatory environment. Elevated levels of TNF-α and IL-6 characterized this pro-inflammatory environment, critical in sustaining the chronic inflammation observed in HS.[83] The therapeutic modulation of miR-146a-5p could attenuate these inflammatory processes and alleviate disease symptoms.

miR-155

Overexpression of miR-155 in HS links disrupted cytokine networks involving TNF-α and various interferons, crucial for innate and adaptive immunity. miR-155 targets signaling proteins and transcription factors that govern cytokine expression and immune cell function, thereby contributing to the chronic inflammatory landscape of HS.[29] Targeting miR-155 could thus offer a therapeutic strategy to reduce inflammation and manage disease progression effectively.

miR-338-5p

miR-338-5p is significantly upregulated in HS and is associated with increased cytokine production and disease severity, suggesting it has a role in HS pathogenesis.[29] The overexpression of miR-338-5p may enhance cytokine signaling pathways, making it a valuable biomarker for disease activity and a potential target for interventions to reduce cytokine-mediated inflammation.

Targeting miRNAs such as miR-155 and miR-223 with synthetic mimics or inhibitors represents a novel therapeutic approach for HS. Modulating these miRNAs may adjust the inflammatory responses and improve clinical outcomes in HS patients. This strategy holds promise for symptom management and fundamentally altering the course of the disease, highlighting the potential of miRNAs in revolutionizing HS treatment.[5,92]

The application of miRNAs as biomarkers in HS presents a novel and promising avenue for noninvasive diagnostics, facilitating early detection and effective coding RNAs such as miRNA-132, miRNA-200c, miRNA-30a-3p, miRNA-100-5b, miRNA-155-5p, and miRNA-338-5p. These RNAs are dysregulated in HS, suggesting their potential as therapeutic targets or biomarkers for disease activity and progression.[86] Biomarkers could optimize patient management, enabling customized treatment plans based on distinct miRNA profiles that predict clinical outcomes and disease progression.[86] Figure 2 depicts the role of miRNAs in regulating the inflammatory pathways involved in HS.

Moreover, the integral role of miRNAs in modulating inflammatory and immune responses enriches our comprehension of HS pathogenesis, catalyzing the development of innovative therapeutic and diagnostic approaches. The ongoing research into miRNA-target interactions, particularly their functional impacts, is vital and may yield substantial progress in HS treatment, enhancing precision and efficacy in clinical applications.

Additionally, emerging research on epigenetic mechanisms underscores the significant role of DNA methylation and histone modifications in regulating genes that orchestrate immune responses and inflammation in HS.[86] Alterations in methylation patterns and histone acetylation at specific inflammatory gene loci exacerbate HS's chronic inflammatory

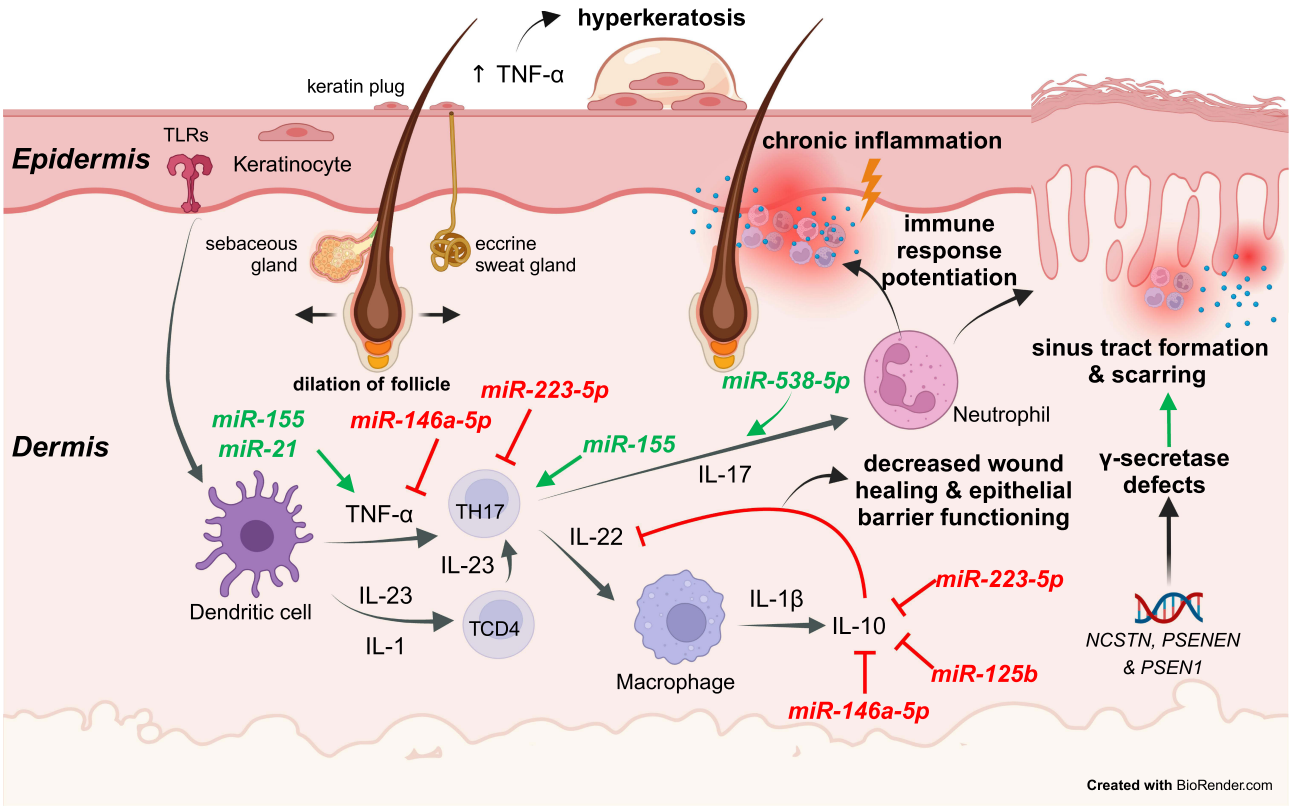

Figure 2 The molecular and cellular mechanisms in the pathogenesis of Hidradenitis suppurativa (HS) highlight the roles of specific microRNAs (miRNAs) and cytokines. The epidermis and dermis depict keratinocytes with Toll-like receptors (TLRs), sebaceous and eccrine glands, and various immune cells.[93] Keratinocyte activation via TLRs in the epidermis increases TNF-α production, causing hyperkeratosis and follicular occlusion with keratin plugs.[93] Dendritic cells in the dermis secrete TNF-α, IL-1, and IL-23, activating TH17 and TCD4 cells, which produce IL-17 and IL-22, driving inflammation and keratinocyte proliferation.[94,95] Macrophages produce IL-1β, while neutrophils accumulate due to chronic inflammation, potentiating the immune response and contributing to tissue damage.[95] Key miRNAs regulate this network: miR-21, miR-155, and miR-146a-5p enhance TNF-α production (green); miR-146a-5p and miR-223-5p inhibit TH17 cells and IL-10 production, disrupting immune regulation; miR-538-5p attenuates IL-17-mediated inflammation; miR-125b inhibits IL-10, exacerbating inflammation (red).[29,82] Follicular occlusion and immune dysregulation drive chronic inflammation and lead to sinus tract formation, scarring, and decreased wound healing due to epithelial barrier dysfunction and impaired immune regulation. Genetic defects in γ-secretase components (*NCSTN, PSENEN, PSEN1*) contribute to these pathological outcomes.[96] This intricate balance of pro-inflammatory and regulatory pathways, disrupted in HS, suggests potential therapeutic targets in miRNA modulation to restore immune homeostasis and mitigate disease pathology. (Adapted from Preda-Naumescu et al,[97] referencing the models of Goldberg et al,[98] Jiang et al,[99] and Chopra et al[100]). Created in BioRender. Ames, E. (2024) BioRender.com/n39w950.

state characteristic, suggesting a profound epigenetic influence on the disease's clinical manifestations. DNA methylation changes may modify miRNAs' expression profiles, impacting cytokine production and the recruitment and activation of inflammatory cells.

Expanding on the role of epigenetic mechanisms in HS, recent studies have revealed that long non-coding RNAs (lncRNAs) modulate inflammatory pathways by interacting with mRNAs identified a regulatory network involving lncRNAs such as *TINCR, RBM5-AS1*, and *MRPL23-AS1*, which interact with mRNAs to modulate immune responses.[101] These lncRNAs are significantly upregulated in HS patients compared to healthy controls. Their findings suggest a coordinated regulation between lncRNAs and mRNAs involved in cytokinesis, maintenance of cellular morphology, tissue development, and progression of HS.[99] Notably, lncRNA-TINCR interacts with mRNAs involved in the regulation of the RhoA and STAT3 signaling pathways, which are both involved in the development of HS lesions. Additionally, mRNAs linked with lncRNAs in the glucocorticoid receptor signaling/STAT3 and macrophage alternative activation signaling pathways, involving genes like IL-13, contribute to cell growth, differentiation, and apoptosis[101] Although limited by a small sample size, these new findings reveal that altered gene regulation within the lncRNA-mRNA network may play a role in HS pathogenesis.

Targeting these regulatory networks at the RNA level could lead to more personalized and effective treatments. Radhakrishna et al (2024) identified 15 lncRNA genes exhibiting differential methylation patterns in HS patients, supporting the role of epigenetic modifications in regulating inflammatory and reparative processes.[102] This study identified hypermethylated and hypomethylated lncRNAs in HS patients, including *DLEU2, TUG1*, and *PCA3*. These lncRNAs are involved in immune regulation, mitochondrial function, and inflammation. *TUG1* is a regulator of the NLRP3 inflammasome, and its knockdown reduces the production of proinflammatory cytokines such as IL-1β. Hypermethylated lncRNAs such as *HAR1A*, which are involved in atopic dermatitis, highlight potential shared genetic pathways between HS and other chronic inflammatory skin diseases. Despite this study's limited sample size, the discovery of differently methylated lncRNAs presents new insights into the molecular mechanisms of HS. It demonstrates the potential for these lncRNAs to serve as biomarkers or novel therapeutic targets for HS management.[102]

Addressing Inequities and Advancing Therapeutic Research in HS

Hidradenitis suppurativa disproportionately affects Black Americans, who experience a threefold higher prevalence and more severe symptoms than White Americans.[103] People of color often face delays in diagnosis, access to specialized dermatological care, and delayed management. Additionally, these racial disparities extend into clinical research, with the underrepresentation of minority populations. In clinical trials involving HS, Black Americans made up 14% of study participants, whereas White Americans made up 68%, limiting the effectiveness and reliability of treatments for diverse racial and ethnic groups. Addressing these disparities is crucial for the future development of HS management.[103] Education among patients and healthcare providers is essential to ensure early diagnosis and treatment, reducing the disease burden on patients.

Despite the availability of systemic treatments, many patients continue to exhibit resistance. The diagnosis is often significantly delayed, with patients typically seeing multiple physicians before receiving a proper diagnosis. Misdiagnosis and lack of awareness among healthcare providers contribute to these delays, worsening patient outcomes.[22] In addition, exploring novel therapeutic targets is a continual need. Recent studies into the immune dysregulation of HS have focused on understanding the roles of various cytokines, including tumor necrosis factor-α, IL-1β, IL-10, and the interleukin pathways involving IL-23/T-helper 17 and IL12/Th1. These studies have been instrumental in creating new treatment strategies. Laser therapies are effective in the short term, offering promising results with acceptable safety and tolerability.[104] The continued pursuit of novel treatments remains essential for optimizing treatment for HS patients.

The role of specific miRNAs in regulating vital inflammatory pathways in HS is a burgeoning field. Further studies should explore the therapeutic potential of miRNA mimics or inhibitors to determine their effectiveness and safety in clinical settings. Hessam et al's use of qRT-PCR to evaluate the expression levels of selected miRNAs in lesional and perilesional skin samples contributes valuable insights. However, the small sample size, including only 15 hS patients and 10 healthy controls, may limit the generalizability of the findings. Larger-scale tissue-specific studies are necessary to understand miRNA roles in HS more precisely. Other methodologies, such as gene expression analysis and methylation

studies, can identify miRNAs that could serve as biomarkers and therapeutic targets. This approach provides a comprehensive view of miRNA involvement in HS but requires validation across different populations and settings.[27] More extensive cohort studies and randomized controlled trials are needed to validate these findings and ensure their applicability in broader clinical settings. Radhakrishna et al (2022) highlighted the role of methylated miRNAs in HS, suggesting that epigenetic modifications could provide new therapeutic avenues.[27] Future research should focus on understanding these modifications and their impact on miRNA function and HS pathogenesis.

The impact of epigenetic changes on gene expression in HS is still emerging. Research into how specific DNA methylation patterns and histone modifications influence disease progression and response to treatment could uncover new therapeutic targets and strategies. Continuing exploration and refinement of these and other emerging treatments will be crucial to enhance their effectiveness and develop long-term management solutions for HS.

Concluding Insights: Elucidating Pathophysiology to Advance Treatment Strategies for HS

Hidradenitis suppurativa (HS) is a chronic inflammatory disease with complex pathophysiology driven by dysregulated inflammatory pathways, genetic predispositions, and environmental factors. Central to this process are inflammatory mediators like TNF-α, IL-1β, and the IL-17/IL-23 axis, all of which contribute to disease progression. Recent studies have focused on miRNAs as crucial regulators in these inflammatory pathways. Dysregulation of specific miRNAs, such as miR-24-1-5p, miR-146a-5p, miR-338-5p, and others, has been shown to influence HS's pathogenesis, offering potential as both biomarkers for early detection and novel therapeutic targets.

Targeting miRNAs in HS presents a new frontier in disease management. The role of miR-146a-5p in regulating TNF-α, miR-155 in cytokine networks, and miR-338-5p in inflammatory signaling highlights their therapeutic potential. Modulating miRNA activity through mimics or inhibitors could help reduce inflammation and disease severity. Furthermore, miRNAs could serve as non-invasive biomarkers, allowing for earlier diagnosis and personalized treatment approaches tailored to each patient's miRNA expression profile, potentially improving clinical outcomes.

In addition to miRNA-based therapies, current treatments like biologics, JAK inhibitors, and surgical options remain vital in managing moderate to severe HS cases. Yet, variability in patient responses indicates a need for personalized care incorporating genetic and miRNA profiling. Lifestyle changes and advanced diagnostic tools like wearable biosensors for miRNA monitoring may optimize treatment outcomes by addressing the environmental triggers and chronic inflammation associated with HS.

As research into miRNA dysregulation deepens, these small, non-coding RNAs are pivotal in the development and progression of HS. Future studies focusing on miRNA-targeted therapies and their integration into clinical practice offer a promising direction for more effective and precise treatment strategies. By unraveling the complex interactions between miRNAs and inflammatory pathways, we can improve diagnostic and therapeutic interventions, ultimately enhancing the quality of life for patients with this debilitating condition.

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Disclosure

The authors report no conflicts of interest in this work.

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