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Advances in Molecular Pathogenesis of Hidradenitis Suppurativa: Dysregulated Keratins and ECM signaling

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Abstract

Hidradenitis suppurativa (HS) is characterized by deep-seated, highly inflamed, and painful lumps/abscesses, fistulae, and sinus tracts that grow extensively deep in the dermis and are highly immunogenic in nature. Evidence for the role of γ-secretase mutations along with dysregulated Notch signaling in HS is strong in about one-third of the HS patients, however, the role of dysregulated Notch signaling in HS pathogenesis in relation to hair follicle alterations and

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hyper-activation of the immune system remains undefined. GWAS, proteomic data and functional investigations of identified sequence variants in HS pathology are not fully revealing. The disease initiation or progression may involve bacterial infection besides defects in the intrinsic functions of keratinocytes, which may be key to further exacerbate the immune infiltration and cytokine production in and around the lesional tissue. The unavailability of a suitable animal model that could fully recapitulate the pathogenesis of HS is a major impediment in the complete understanding of the underlying mechanisms and development of effective treatments. Dysregulation in keratinocytes, dermal fibroblasts and the presence of extracellular matrix (ECM) degradation products that ultimately affect immune regulation are key components of HS pathogenesis. Bacterial infection further exacerbates the complexity of the disease progression. While anti-TNFα therapy shows partial efficacy, no effective treatment is available to cure HS. Multiple clinical trials targeting various cytokines, complement C5a and ECM products are in progress. This review provides updated information on some of these aspects with a focus on dysregulated keratinocyte and immune cells and role of ECM, and Keratin functions in this regard.

1. Introduction

HS is a chronic, inflammatory, recurrent, debilitating skin disease (of the terminal hair follicle) that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital regions [1]. The quality of life (QoL) is highly compromised in HS patients and social embarrassment along with physical distress are frequently observed in these patients [2, 3]. In addition, many HS patients have a higher risk for developing other diseases such as hypertriglyceridemia, HDL-cholesterolemia, obesity, cardiovascular disorders, back pain, axial spondyloarthritis, and reduce life expectancy [4–6].

Early pathogenesis involves follicular hyperkeratosis and lymphocytic perifollicular and sub-epithelial inflammation. However, clogging of the hair follicle with keratin and secretion of sweat glands followed by its rupture and bacterial infection are the key events associated with the progression of the disease [7]. It is believed that hair follicles filled with keratin, secretion of sweat glands, and bacteria cause mechanical pressure leading to their disruption. The material that pours out of the ruptured hair follicle spreads to nearby hair follicles. As additional hair follicles continue to clog and burst, lumps are formed, which then lead to the formation of the deep tunnels inside the dermis [8, 9]. The skin at this stage of disease progression shows painful nodules and swollen lumps filled with pus (abscess). Furthering of this process involves healing and reappearance of lumps that leads to scarring. The bacterial infection triggers activation of inflammatory pathways and alters host-pathogen interactions characterizing the cutaneous inflammatory process [10, 11]. The early HS lesions could originate from ORS epithelial cells particularly derived from infundibulum of hair follicle. It was considered important in the formation of tendrils, which extend over the adjacent soft tissues [9].

Histologically, the inflammatory process in the epidermal compartment of HS skin is derived from psoriasiform hyperplasia [12]. Tunnels isolated by microdissection had higher levels of epithelial tissue-derived production of inflammatory cytokines relative to the normal

epidermis of healthy controls. Decrease in the size of draining tunnels following treatment with IL17RA antagonist Brodalumab and around 50% reduction in active nodule (AN) count without increase in abscesses or draining fistulae by TNFα antagonist Adalimumab, showed a crucial role of inflammation driven by these cytokines in HS pathogenesis [13, 14]. Moreover, mutations in the classical autoinflammatory genes involved in systemic autoinflammatory diseases (SAIDs) such as MEFV, NLRP3, NLRP12, NOD2, LPIN2, and PSTPIP1 also suggest their role in augmenting inflammation in HS [15]. Mutations in inflammasome genes, the main inflammatory component of innate immune cells have been linked to the enhanced inflammatory cytokine release such as IL1β, IL17, IL18, and IL23. SNPs at the 238-promoter region of the TNFα gene were positively associated with predisposition to the HS [15].

Alterations in Vitamin D metabolism, keratinization, formation of the cornified envelope, and steroid metabolism and biological process associated with collagen and extracellular matrix remodeling are also equally important in uncovering the complex pathogenesis of this disease [16]. An important observation in this regard, is early onset of dilation in the hair follicle, lack of hair shaft, which had thin hair sheath, with the formation of dermal cysts containing tissue debris similar to that observed in the early phase of HS pathogenesis in homozygous KO mice lacking Vitamin D Receptor (VDR) [17]. Furthermore, these mice showed reduced expression of involucrin, proflaggrin, and loricrin, the epidermal differentiation markers from birth until 3 weeks. However, the Keratin-10 expression was not changed. These VDR KO mice had a high number of small dense granules in the granular layer with reduced keratin bundles and keratohyalin granules. These data provide important role of vitamin D signaling in HS. However, further data is needed to exactly demonstrate its role.

The majority of HS clinical trials rely on drugs developed against various other inflammatory skin diseases/disorders such as Psoriasis [18]. For instance, anti-TNFα therapy is the only FDA-approved therapy for HS and psoriasis, however, both of these skin diseases only partially respond to the treatment. Unlike psoriasis, which is a better-defined skin condition, the immuno-biology of HS is poorly understood except both diseases have transcriptional overexpression and translational elevation of some proinflammatory cytokines/chemokines [19]. Furthermore, the exact diagnosis and prognosis are also be difficult to achieve without the mechanistic understanding of HS. In this review, we discussed and correlated various aspects of already described HS pathogenesis and underlying cellular and molecular signaling events and associated mechanisms as summarized in Figure-1. This review also identifies gaps in these published investigations while linking various independent investigations to disease pathogenesis.

2. Dysregulated immune system and HS

An epidermal hyperplasia and intrusion in the dermal components along with elevated infiltration of various immune cells were observed to be associated with various stages of HS disease progression [20, 21]. Witte-Handel *et al.,* demonstrated that interaction of various cytokines to different cell types such as keratinocytes, fibroblasts, endothelial cells, and PBMs could further exacerbate inflammatory cascade and ECM remodeling. After

exposure with various cytokines such as IL1β, IL17, IL19, IL22, IL24, TNFα, and IFNγ to fibroblasts and keratinocytes, IL1β was able to induce MMP3, CXCL1, and IL6 in fibroblasts, while MMP10 and CXCL1 in keratinocytes. None-the-less, other cytokines such as IL17 and TNFα were also able to induce these cytokines/chemokines in both fibroblasts and keratinocytes. It is interesting to note that immune cells, endothelial cells, keratinocytes, and fibroblasts all respond similarly to IL1β for upregulating molecules involved in ECM remodeling, neutrophil migration, and production of immune-modulatory chemokines. ECM remodeling by IL1β was associated with the enhanced production of various matrix metalloproteinases (MMPs) such as MMP3, MMP10, and enzymes ADAM12, protease inhibitors like Serpin A1, and matrix components such as collagen Type-IIIα1 (COL3A1), COL10A1 [21]. In the following sections, we discussed the role various components responsible for the progression of inflammation associated with HS.

2.1. Keratinocytes

Keratinocytes isolated from the skin outer root sheath cells (ORSCs) of HS patients manifested hyper-inflammatory signatures. In this regard, higher production of IP10, CCL5 (RANTES), and IL1β was observed in supernatants of ORS-keratinocytes from the HS patients relative to supernatants of ORS-keratinocytes from the healthy subjects. Moreover, after stimulation with IL1β, relative to keratinocytes isolated from the healthy donors, the secretion of other chemokines/cytokines such as IL6, IL8, and TNF-α, in addition to IP-10, and CCL5 was elevated in ORS-keratinocytes from the HS patient. Similarly, the steady-state expression of S100A7 (psoriasin), RNase7, and S100A8 was increased, while the expression of the hBD-1 gene was impaired in HS keratinocytes. Treatment of Pam2CSK4 and muramyl dipeptide (MDP) significantly increased expression of S100A7 and S100A8 genes in ORS-keratinocytes from a healthy donor, but these responses were absent in ORS-keratinocytes from the HS patient. Furthermore, the expression of hBD-1 was significantly reduced after the MDP stimulation in ORS-keratinocytes from the HS patients relative to ORS-keratinocytes healthy controls. These intrinsic functional defects in keratinocytes, which failed to respond properly against various challenging conditions point to impairment in the first line of defense against pathogens in the HS skin. Neutrophils and macrophages express S100A8/9 while an increase in the heterodimers of these proteins in serum could serve as an important biomarker for disease pathogenesis [11]. Subclinical inflammation could promote plugging and occlusion at the level of the infundibulum of HFs followed by cyst development at an early stage of disease progression. However, the deep dermal infiltrate is likely to evolve at the later phase of disease progression [7, 11].

Deficiency in Notch signaling could be involved in the intrinsic defects of HS keratinocytes, which may further initiate a pro-inflammatory cascade of chronic inflammation in the HS skin [20]. Mutations in genes of the Notch pathway in HS patients orchestrate defect in skin homeostasis by switching programming between cell proliferation and differentiation processes and could be a key factor in disease progression [22]. It may also result in impaired mitogen-activated protein kinase (MAPK) phosphatase 1 (MKP-1) signaling, which is required for the feedback inhibition of proinflammatory MAPK pathway for cytokine production.

Orvain et al. recently described the involvement of HF stem cells (HFSCs) in proliferating progenitor cells with a loss in quiescent stem cells, isolated from the ORSCs of HS patients. These authors demonstrated that ORSCs from HFs of HS patients have faulty replication fork and manifest activation of the ATR/CHK1 pathway. Furthermore, the activation of ATR/CHK1 signaling was associated with enhanced cytoplasmic ssDNA. Thus in the HS Skin, ssDNA sensing leads to the activation of the IFI16/STING pathway and enhanced production of type I IFNs [23]. These findings highlight that faulty intrinsic cell properties with enhanced replication stress and the DNA damage response are closely associated with the pathophysiological process of HS disease progression, while changes in the local microenvironment associated with bacterial infection are relatively less relevant. Moreover, these self-perpetuating mechanisms have also been linked with enhanced local inflammation, which may lead to enhanced ROS production and could contribute to genotoxic insults and genomic instability [23].

The replication stress and genomic DNA damage may trigger an inflammatory response through the accumulation of cytosolic DNA fragments and aberrant STING signaling. Cytosolic DNA can be generated either via dysregulated DNA repair activity or by the rupture of micronuclei, which are formed during mitosis because of broken or lagging chromosomes. Under replication stress conditions, chromosome missegregation may occur due to faulty replication and/or by NHEJ-mediated chromosome rearrangements, which may encounter the buffering capacity of TREX1, an exonuclease. The loss of TREX1 is associated with type I IFN induction [23]. Aberrant cGAS-STING–mediated type I IFN secretion has been reported in multiple diseases such as myocardial infarction [24], fibrotic interstitial lung disease, and auto-inflammatory diseases such as the immunodeficiency syndrome ataxia-telangiectasia due to genetic deficiencies in DNA damage response gene, ATM. Many studies have reported the phenotypic heterogeneity in HS patients and correlated it with many heterogeneous pathogenic pathways. 75% of HS patients (6 out of 8) had demonstrated higher replication. The replication stress was found in S phase cell cycle (>25%), where alteration of replication fork progression and increased proportion of cells with γH2AX foci (>9%) were noticed [23].

Marohn et al. carried out a single-cell analysis and identified various types of keratinocytes in the HS skin. The keratinocytes lining of HS sinus tracts expressed a number of genes specific for apocrine sweat glands and sebaceous glands [23]. However, their morphology and differentiation pattern were matching to the interfollicular epidermis. These data support that epidermal stem cells residing in the infundibulum have cell fate duality, while loss of SOX9 (appendage fate TF) could trigger epigenetic reprogramming, which could further be involved in stimulating the formation of sinus tracts with some glandular signature and features resembling interfollicular epidermis [25].

2.2. Neutrophils

Neutrophils infiltration in HS skin lesions is very prominent, but its exact role in the initiation and/or progression of disease pathogenesis is still unclear. In this reagrd, enhanced number of T helper (Th17) cells with high levels of IL17 in skin lesions also indicate the involvement of neutrophils migration and local tissue damage. Neutrophil derived cytokines

such as IL1β, IL6, IL17, and IL23 are associated with specific gene expression signatures involved in epidermal hyper-proliferation and abnormal differentiation of keratinocytes. Neutrophils often exhibit NETosis, a phenomenon in which neutrophils form web-like structures known as neutrophil extracellular traps (NETs). Nucleic acid, granules, and cytoplasmic proteins are used to generate these NETs to trap microbes in extracellular space [26]. Since, HS lesions have bacterial infection; the NETosis seems to be a likely mechanism to control fast pathogenic bacterial growth in the lesional skin. Byrd and colleagues reported that neutrophils isolated from the peripheral blood of HS patients show enhanced spontaneous NETs formation relative to neutrophils procured from healthy controls [27]. The enhanced NET formation by circulating neutrophils could further induce the cutaneous plasmacytoid dendritic cells (pDCs)-mediated type I IFN and associated signaling in localized skin lesions. However, no systemic type I interferon response could be observed, as the NET complexes in the circulation of HS patients were not enhanced [26]. The observed NETs forming neutrophils *in vitro* from peripheral blood could be due to the transmigration of HS lesional neutrophils into circulation as their numbers could be correlated with the pathology of various Harley Stages of the disease. Moreover, autoantibodies against the citrullinated histone/NETs could be detected in serum samples of HS patients [27]. In many auto-inflammatory and autoimmune diseases, NETs have been reported to exacerbate aberrant innate and adaptive immune responses including the induction of Type I interferon and activation of inflammasome pathway [28]. Autoantibodies represent both the aberrant NETs formation and impaired NETs clearing.

2.3. Macrophages and DCs

While NETosis is known to be in neutrophils, other cell types including monocytes and macrophages are also able to release extracellular traps of DNA and other proteins such as histone, myeloperoxidase, and lysozyme. This phenomenon in other immune cells is known as METosis. METosis is not studied in HS, but bacterial infection along with abundant infiltration of macrophages in HS lesions indicate some key roles of macrophages in HS pathobiology. Macrophages are not only important in elaborating innate immune response but could also play significant roles in adaptive immune responses particularly, by producing cytokines like IL23 [29], IL1β [30] and TNFα, as observed in HS patients. Although some recent investigations showed that IL17 could be produced by neutrophils [31], but IL23-IL17 pathway axis could also be elaborated by macrophage in the HS [32]. Mainly synthesized in activated macrophages, TNFα is considered as “master-inflammatory regulator cytokine” in HS, which play synergistic role with IFNγ to induce expression of several mRNAs such as interferon regulatory factor-1 (IRF-1), intercellular adhesion molecule-1 (ICAM1), MIG (monokine induced by gamma-interferon), and CCL5 (regulated on activation normal T cell expressed and secreted). Moreover, this cooperativity is mediated by synergism between two distinct transcription factors: signal transducer and activator of transcription 1 (STAT1) and nuclear factor kappa B (NFκB).

TNFα, besides being mainly produced by activated macrophages, dendritic cells also have the capacity to produce it [33]. DCs play an active role in the maintenance of peripheral tolerance to self-antigens in the steady state and immature DCs induce IL10-producing regulatory T cells *in vitro* and *in vivo*. Thus, the interaction of immature DCs with T

cells could lead to immune tolerance, while its interaction to mature DCs produce T-cell immunity. IL10 has also been reported to be significantly upregulated in HS lesions, and macrophages could be the primary producer of this vast amount of IL10 [34]. It has been shown that bone marrow-derived macrophages stimulated by efferocytosis (clearance of apoptotic neutrophils), and characterized by high IL10 production, produce TNF-α following re-stimulation with LPS [35]. Although, there is no consensus on IL10 producing macrophages in the HS, the high number of macrophages and neutrophils in HS infiltrates and abscesses suggest that bacterial products like LPS may stimulate macrophages. As also described earlier, the occult inflammation could drive psoriasiform hyperplasia in the perilesional of HS skin and this could be considered as an important event in the recurrence of disease after surgery. Recently, functionally active pDCs along with up-regulated type I IFN in HS lesions suggest that priming pDCs may be involved in the disease recurrence. Plasmacytoid dendritic cells have their known role in many autoimmune diseases including systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and graft-versus-host disease (GVHD) [36]. Several drugs targeting pDC including anti-interferon-α (anti-IFNα) monoclonal antibody (mAb), anti-type I IFN receptor subunit-1 (anti-IFNAR1) mAb have shown promising outcomes in SLE. However, the therapeutic response of the currently FDA-approved drug Adalimumab to HS is in nearly 40% population and is sub-optimum, which indicates the involvement of additional cell types in the HS pathogenesis [37].

2.4. Plasma cells, B cells and T cells

Recently, Gudhonson *et al.* demonstrated the contribution of plasma cells and B cells populations in the pathogenesis of HS [38]. Their data show that the B cells and the plasma cells associated with enhanced immunoglobin production and complement activation may play a major role in disease pathogenesis. Furthermore, TNFα expression was localized to $CD138^+$ plasma cells. Treatment with Rituximab, a chimeric monoclonal antibody active against CD20 has been successful in the treatment of HS patients with idiopathic carpotarsal osteolysis and chronic active antibody-mediated rejection [39]. In this regard, activation of Bruton`s tyrosine kinase (BTK) and spleen tyrosine kinase (SYK) pathways could be novel druggable targets to treat moderate to severe HS [38]. These pathways have been correlated with plasma cell and B cells infiltration in HS. Thus, B cells could also be blocked by targeting B cell-specific pathways such as BTK, LCK, SYK, and BCR signaling [38]. It remains to be demonstrated if targeting these signaling proteins provides some therapeutic benefits in HS patients.

In an independent study, Lowe *et al.,* performed the principal components analysis (PCA) of the whole-skin transcriptome of 19 HS lesions before TNFα therapy and 16 HS lesion on adalimumab therapy. They demonstrated that lesion transcriptome was shifted to normal healthy control skin, while PANTHER analysis showed preferential reduction in B cell pathway genes [18]. However, in another study, a detailed analysis of skin-infiltrating T cells isolated from skin biopsy samples and blood from HS patients demonstrated that TNFα blockade was associated with inhibition of pathogenic CD166 and IL17 expressing Th17 lineage [40]. They studied T cell populations within the viable $CD45^+$cell population, followed by sequential gating of either $CD3^+\gamma\delta^+$ (γδT cells) or $CD3^+\gamma\delta^-$T cells and either

$CD3^+CD8^+$ (CD8 T cells) or $CD3^-CD8^-$ (CD4 T cells). These authors did not find any noteworthy differences in the frequencies of CD4, CD8, or γδ T cells between lesional, perilesional, or uninvolved HS and control skin. However, infiltration of Th17 cells along with levels of pro-inflammatory cytokines GM-CSF, IL22, IFN-γ, and TNFα was higher in the HS skin. In this study, high infiltration of regulatory T cells in HS lesional skin was also observed; but the ratio of Th17 to regulatory T cells was in favor of Th17 cells. Interestingly, TNFα treated samples reflected reduced infiltration of Th17 cells and normalization of Th17 to Treg cell ratio [40].

2. 5. Activated complement system in HS

The elevated levels of various components of complementary system such as C5a and soluble C5b-9 in the serum of HS patients was observed but it could not be correlated with the disease severity [41]. Treatment with IFX-1, a C5a antagonist enrich blood mononuclear cells with patient plasma, attenuated TNFα production suggesting an active involvement of complement system in the HS pathogenesis. Mechanistically, the C5a-dependent release of TNFα is known in CD11b+ cells and TNFα may further induce complementation activation through the upregulation of C3, down-regulation of CD141, and impaired protein C activation. Treatment with Adalimumab, Infliximab, and Etanercept (anti-TNF agents) reduce the levels of C3 and C4 components in psoriatic and arthritis patients. Hoffman *et al.,* carried out bioinformatics analysis and observed elevated C1q and C2 along with complement receptors CR1, C3aR1 and C5aR1, which further supports the involvement of complement signaling in the HS pathogenesis. Although, it is not yet clear which complement pathway (classic, lectin, or alternative) is involved in the HS, yet the classic pathway seems to be dominated in the HS pathogenesis. This is because C4 protein and immunoglobulins were elevated in the skin and blood of the HS patients [42]. However, a clinical trial using IgG5 antibody against C5a showed modest clinical efficacy in HS [41] questioning the therapeutic significance of altered complement system in this disease.

3. ECM and HS

The ECM is a complex network of proteins and proteoglycans secreted by keratinocytes, fibroblasts, and immune cells. The function of the skin ECM has expanded from being a scaffold that provides structural integrity to more dynamic moieties that constantly remodel over time to maintain tissue homeostasis. The ECM functions as a ligand for cell surface receptors such as integrins, dystroglycans, and TLRs and regulates cellular signaling and immune cell dynamics. The ECM also acts as a sink for various growth factors and cytokines/chemokines, which provide critical cues during epithelial morphogenesis. Dysregulation in the organization and deposition of ECMs could lead to a number of pathophysiological conditions, which could be further exacerbated by the aberrant ECM-immune cell interactions. These data are summarized in table-1. In this section, we focus on the interplay between ECM and immune cells in the context of inflammatory skin diseases with special emphasis on HS pathogenesis.

ECM components such as laminin and collagen peptides act as ligands for various immune cells and facilitate their physical properties and trafficking [43]. In certain conditions, excess

ECM deposition results in the enhanced fibrosis that could later be develop into cancer [44]. Therefore, maintaining a balance between tissue remodeling by the immune system and ECM dynamics is critical to regulating tissue homeostasis.

The HS dermis is known to have extensive cellular infiltration and aggregation as well as disorganized collagen deposits [45]. A repeated cycles of inflammation and healing process seem to affect the normal cyto-architecture, which is associated with increased deposits of type I and type III collagen [45, 46]. The role of M2 macrophages is prominent in collagen deposition, ECM degradation, differentiation of fibroblasts into myofibroblast, and tissue fibrosis. Several studies suggest the involvement of M1 macrophages in HS. However, the role of M2 macrophages ($CD163^+$) is known to be more prominent in chronic HS lesions including in the formation of sinus tract and scarring. $CD163^+$ expressing M2 macrophages have been detected in the dermis of HS lesions [47]. The upregulation CCL18 in $CD163^+$ expressing M2 macrophage stimulates the fibroblasts-mediated collagen production in chronic HS lesions [48]. We also observed the elevated level of IL13 protein and enhanced TGF-beta signaling along with massive infiltration of macrophage (and neutrophils) which suggest that the involvement of these pathways and could lead to enhanced deposition of various collagens such as COL1A1, COL2A1 and COL3A (unpublished data). Sanchez *et al.,* carried out explant culture of skin excised from HS patients and normal controls and analyzed the change in dynamics of collagen and elastin degradation at day 4^{th} of culture. The percentage area of type I and type III collagen was higher in the papillary and reticular dermis of perilesional and HS lesional skin at day 0 of culture relative to normal skin. However, the percentage area of type I collagen in these lesions was reduced following day 4 of culture, but not in normal control skin. The intensity of type III collagen fibers was also reduced in reticular dermis of the HS lesions but remained unchanged in normal skin. Similarly, the elastin levels were higher in HS lesional skin at day 0 of culture relative to perilesional skin. After day 4 of culture the elastin staining were sharply reduced in the HS skin, but not in the perilesional skin. Taken together, this study demonstrated enhanced degradation/fragmentation of elastin fibers in the pathogenesis of HS lesions, which also changed quantity and organization of collagen fibers [46]. Furthermore, at day 0 elevated levels of activated MMP2 and MMP-9 in HS lesional skin were noted but after day 4 of explant culture, the levels of these activated MMPs were comparable between the perilesional and the HS lesional skin. Interestingly, this study did not report any change in IL17 and NLRP3 inflammasome level at day 4 of culture, but IL1β concentration was always high in perilesional and lesional HS skin, which indicate the possible role of MMP-induced matrix alteration in HS inflammation without any external stimuli. Concordantly, the treatment with IL1β to primary human PBMC, microvascular dermal endothelial cells, dermal fibroblasts, and keratinocytes induced molecules involved in ECM remodeling such as various collagens viz., COL3A1, COL7A1, COL10A1, COL16A1, COL24A1, DCN, ELN, NTN1, LAMC3, TNFAIP6, SPON1 and various matrix metalloproteinases namely, MMP3, MMP7, MMP8, MMP9, MMP10, MMP12, MMP14 along with various other cytokines/chemokines [21]. In murine dermal fibroblasts, TGF-β signaling resulted in the activation of SMAD2/3, which, in turn, increased the expression of ECM-related genes such as Col1a1 and Col3a1 [49, 50]. In multiple cancer types, increased fibrosis characterized by accumulation of collagen I and III has been observed [51, 52]. IL13 produced by innate

lymphoid cells stimulated the differentiation of fibroblasts to myofibroblasts and increased collagen synthesis and its accumulation in fibrosis as observed in HS [53]. Interaction of collagen with inhibitory receptor LAIR-1 of immune cells is known to activate them that in turn, may hamper the cytotoxic function of NK cells and T cells. Likewise, increased collagen fibers in chronic HS lesions may also hamper the cytotoxic activity of immune cells, which could further support the observed enhanced bacterial growth, nociception and epidermal proliferation. Collagen can affect the proliferation of other immune cells too. Interaction between collagen-VII with other immune-activating matricellular protein namely, cochlin is known to manifest some anti-pathogenic potential [54], while collagen fragments increase the secretion of IL1β by blood monocytes [55]. Although, these observations are key to design further experiments, a more rigorous experimental strategy is needed to delineate the exact role of collagen regulated signaling defining disease stage-specific activation of immune cells.

Elastin peptides generated from elastin degradation could modulate the innate immune response by exerting chemotactic effects on monocytes and neutrophils just like other chemo-attractants such as FMLP or C5a [56, 57]. Similarly, in HS lesions where elastin fibers degrade, immune cells activation could further exacerbate oxidative stress either via free radical generation or through secretion of elastase and MMPs [58]. Elastin peptides have the ability to bind with elastin receptors presented on the cell surface of human dermal fibroblasts and have the capability to stimulate collagenase-1 expression via the extracellular signal-regulated kinase (ERK) pathway, which could further enhance the cytokine production [59]. At lower concentrations, elastin could not only enhance T-lymphocytes proliferation [60], but could also polarize T cells towards Th1 response and hence has the ability to modulate the adaptive immunity in the initial phase of inflammation onset [61].

Danby et al. investigated the change in the epithelial support structures of the folliculopilosebaceous unit (FPSU) i.e. basement membrane zone (BMZ), sinus tracts (STs), and the interfollicular basement membrane (BM) using periodic acid-Schiff (PAS) staining [62]. Compared with the axillary skin of human controls, the sebofollicular junction in patients with HS did not show any PAS-positive staining in both the border and center lesions of HS, however, staining was uniform at STs and BMs irrespective of inflammation, explaining the apparent fragility of the sebofollicular junction [62]. In another study the expression of the important BMZ components, including type XVII collagen, type VII collagen, laminin 332, and integrin α6β4 of follicular epidermis relative to the interfollicular epidermis of HS were investigated. No significant differences in the levels of collagen and laminin among HS patients and control skin samples were found, but the intensity of β4 integrin was very high in the sebaceous gland in HS patients [63]. Integrins are known to be involved in the organization of the basal keratinocytes' BM components [64]. Integrins have α and β subunits and there are 18 α and 8 β subunits, which have the capability to arrange in 24 different types of combinations. However, α2β1, α3β1, and α6β4 are the main integrin pairs expressed in the skin [65]. Integrin β4 and β1 are the components of hemi-desmosomes junctions and focal adhesions which facilitate the adherence between keratinocytes and underlying BM either through intermediate filaments at hemidesmosomes junctions or via actin cytoskeleton network at focal adhesions (FAs) [66].

ECM-integrin signaling is required for several vital processes including cell proliferation, cell differentiation, cell adhesion, cell migration, and apoptosis [67]. The loss of integrin β1 in embryonic skin resulted in enhanced degradation of ECM components, which further exacerbates inflammation [68]. β4 integrins are predominantly found in the BMZ area of the skin and provide adhesive function. Apart from this, the interaction of these integrins with various other proteins is crucial for the activation of various signaling pathways. Dysregulated interactions are associated with involvement in various pathologies including oncogenesis and inflammatory immune response. Recently, heterozygous mutations in the ITGB4 gene encoding integrin β4 protein were found to be associated with junctional epidermolysis bullosa with pyloric atresia (JEB-PA). Immunofluorescence mapping of EB patient`s skin revealed a sub-epidermal blister with decreased and frayed integrin β4 at both the floor and the roof of the blister, while the intestinal mucosa showed a complete absence of integrin β4 [69]. Upregulation of α6β4 was also seen in bacterial infection of pulmonary tissue. These integrins may function as pattern-recognition receptors (PPRs) which may induce innate immune response during bacterial infection such as that observed in HS. However, exact dynamics and role of integrins proteins and associated signaling remains to be uncovered in the HS pathogenesis. Finally, enhanced expression of α6β4 integrins is also possibly found to be involved in squamous cell carcinoma (SCC), which is also associated with the HS especially in African American population [70, 71]. These observations are important to be investigated in future studies particularly, to understand the regio-specific propensity of the HS cells to transform into neoplasm.

Although there is no concrete data about fungus infection in the HS, however, fungi interact with dermal ECM component fibronectin (Fn) and could also result in perpetual onset of inflammation that may further contribute to fibrosis [72]. Abundant fungal spores within the hair shafts at inflammatory lesions are found in human skin specimens of active HS. Treatment of HS fibroblasts to fungal β-glucan or Fibronectin significantly induced MMP2 activity, while fibronectin was also able to induce IL8 mRNA and IL6 release [72]. The disrupted laminin layer within the BM in psoriatic skin has been reported to be associated with increased expression of extradomain A+ fibronectin (EDA+ FN) and α5β1 in basal keratinocytes. These keratinocytes could proliferate in response to various stimuli, and continuously elaborate plasminogen activation enzymes, known to digest laminin. Laminins have a critical role in structural support and are a major component of the BM that separates endothelia and epithelia from the underlying tissue. About sixteen isoforms of laminin have been identified, which have distinct functions and tissue expression. Recent evidence support that these isoforms directly interact with immune cells. Most leukocytes express laminin-specific receptors, suggests that laminins have the ability to modulate their proliferation, activation, migration or survival responses [43]. Elevating laminin-511 expression in HaCat cells was able to enhance epidermal proliferation with reduced apoptosis, which could provide one of the mechanisms of epidermal hyperplasia in psorioform lesions as occur in psoriasis and HS as well [73]. Alteration in laminin α1 chain together enhanced fibronectin and lymphokines in involved and uninvolved HS lesion, suggest its role in creating abnormal cellular morphology. While laminins have been shown to exacerbate neutrophil infiltration and phagocytic ability of dendritic cells, their role in immunomodulation in the HS remains poorly described.

Other ECM components such as Extracellular matrix proteins 1 (ECM1) were also dysregulated in the HS. ECM1 is an 85-kDa glycoprotein involved in skin physiology, angiogenesis etc. ECM1 can interact with αv integrins on dendritic cells and could block the latent TGF-β activation, resulting in an inhibition of Th17 cell differentiation. Several other growth and tissue factors such as Tissue factor3 (T3), Growth and differentiation factor 2 (GDF2), Midkine and Clusterin are suppressed in HS lesional skin relative to normal control [42, 74]. These growth factors play important roles in vital cellular processes including growth, differentiation, metabolism and clearance of debris [75]. However, their role in the HS pathogenesis is largely unknown and needs to be investigated.

4. Keratins and HS

Keratins belong to a superfamily of intermediate filament (IF) proteins and make around 85% portion of fully differentiated keratinocytes [76]. Heteropolymeric keratin filaments contain α-helical coiled-coil domain, non-helical head and tails domain having many phosphorylation sites [77]. Around 54 keratin genes are expressed in a highly specific manner on epithelial tissues and around half of them are expressed in hair follicles during various stages of growth, development, and differentiation. In the form of tonofilaments, keratin bundles and binds with cytoplasm, desmosomes, and other cell structures [78], which reflects their primary function to provide mechanical stability and cellular integrity for cells and epithelial tissues [79]. Mutations in keratin genes have been known to cause disarrangement in the cytoskeleton and various hereditary keratinization disorders such as epidermolysis bullosa, congenital ichthyosis, and palmoplantar keratoderma [80]. As the outermost layer of the body, the epidermis is exposed to a harsh environment, which contains diverse challenging insults including infections, antigens, mechanical stimuli, and environmental chemicals. Interestingly, the underlying protective biochemical mechanisms are also evolved to combat these multifarious strong stresses. However, these powerful armory fail during disease progression for reasons largely unknown.

Normally, keratins, K5 and K14 are expressed in the basal proliferative layers, while keratins, K1, and K10 are expressed in suprabasal differentiating layers of the epidermis. However, in various inflammatory diseases such as psoriasis and atopic dermatitis, the expression pattern of keratins are changed significantly. Expression of inflammatory keratins such as K6, K16, and K17 is induced while expression of K1 and K10 is downregulated. In this regard, EGF signaling is involved in elevating the levels of K6 and its counterpart K16 [81]. Various cytokines such as TNFα-induce K6 promoter activity through NFκB and C/EBPβ pathways [82], while IFNγ regulates K17 promoter by STAT1 pathway [83]. In addition, IL1β could also modulate K6 through C/EBPβ while IFNγ could modulate K6 through STAT1 signaling. These signaling pathways are significantly altered in the lesional and peri-lesional skin of HS patients.

In immuno-histochemical analysis of keratins in the skin samples from 14 HS patients, Kurokawa *et al.* observed a normal expression of K1 and K14 while expression of K17, K16, and K19 was absent in infundibular keratinized epithelium with keratohyline granules (Type A, HS lesion), though it was very high in the infundibulum and sebaceous ducts of the normal skin [84]. K1, K10, and K19 were negative while the expression of K14 was present

but with uneven staining patterns. K16 and K17 were present in the suprabasal layer in other types of non-infundibular keratinized epithelium without keratohyline granules (Type B) of HS skin. Structurally distinct position of the non-keratinized epithelium (Type C) of the HS skin was associated with the absence of expression of K1, K10, and K19 and strong expression of K14 in all the layers. A moderate expression of K16 and K17 was observed in the suprabasal layer. Moreover, relatively weaker staining of K1 and K10 was observed in the suprabasal layer of acanthotic epidermis overlying sinus tracts than that of the normal skin. K17 is a hyper-proliferation marker, and have characteristics of spatial keratin. K17 present on type A epithelium could represent fragile follicle; which after rupture may lead to the development of subcutaneous abscess [84]. K15 is a marker for the presence of stem cell, has variable, but more intense expression at basal layer of epidermis in HS skin [9]. Zouboulis *et al.,* studied transcriptome profiling of lesional and non-lesional skin obtained from female HS patients and matched healthy control using Agilent array platform. An upregulation of various keratin genes such as K16, K6A, K6B and K6C along with GJA2 (Connexin-38) was found in the lesional skin relative to the non-lesional skin of the same patients. Furthermore, the expression of most keratin genes including K16, K6A and GJB2 (Cx32) was amplified more significantly when lesional skin was compared with the control skin of healthy donors [85]. K16 and K6 being markers of hyper-proliferation suggest the hyper-proliferative nature of epithelium in HS lesions. Type I cytokeratin K16 and Type II cytokeratin K6A have paired in many tissues including HFs. The *de novo* transcription of these keratins have been reported to be induced in the stressed keratinocytes. Because of specialized function in the progression of inflammation, cytokeratins such as K6, K16, and K17 have also been found upregulated in various inflammatory diseases like psoriasis as well as skin wounds [86, 87]. Pathway analysis using gene Enrichr, showed significant enrichment of genes associated with keratinocyte-specific expression [85]. Notably, K6A and K16 are also expressed in secretory and luminal cells of eccrine sweat gland and their increased expression was not due to the enhanced number of these glands. The expression of K77, which exclusively expresses in eccrine sweat glands, K73, and K74, which are specific to the HF, are downregulated in HS lesions [79, 88].

Dysregulated Notch signaling promotes conversion of the HF to keratin-enriched epidermal cyst followed by infundibular hyperkeratinization and follicular occlusion at early stages of HS progression [89]. Aberrant Notch signaling has also been linked with the upregulation of proteins involved in the development of cornified envelop (CE). In this regard, overexpression of SPPR1B, SPRR2D, SPRR3, and IVL resulted from damage CE in the skin lesion in patients affected with Dowling-Degos disease with hidradenitis suppurativa (DDD-HS) [90]. The upregulation in the expression of SPRR and IVL genes has also been reported in psoriasis [91]. Enhanced expression of SPRR3 in apocrine sweat gland ducts and sebaceous glands has been found in HS patients, which indicates the active involvement of these glands in the disease pathogenesis [85]. Altered barrier function and elevated SERINB3 and SERPINB4 have been observed in the HS skin. Overexpression of SERPINB3/SERPINB4 has been shown to protect against ultraviolet and γ-radiation exposure as well as TNFα-mediated apoptosis. The expression of these proteins has also been shown to be elevated in the skin and serum samples of psoriasis and AD patients [85]; however, their involvement in compromised barrier function in HS pathobiology remains

unclear. The side-by-side comparison with other chronic inflammatory diseases or other skin conditions in which inflammation plays a critical role provides a clear understanding of overlap and departure of roles of these keratins and their regulatory pathways in HS disease progression. This comparison further ascertains the need to dig into some of these pathways to uncover the complexity associated with stage-specific progression and intervention of HS.

5. Currents Clinical trials

A large number of biologicals as well as small molecules are under clinical trials in search of highly effective treatment for HS. These therapeutics mainly target TNFα (Adalimumab, Infliximab, Golimumab), IL1 (Anakinra, Canakinumab, MABp1/bermekimab), IL12/IL23 (Ustekinumab, Guselkumab), IL17 (Secukinumab, CJM112, Bimekizumab), Complement system (IFX-1) and JAK/STAT pathway (Tofacitinib, Baricitinib, INCB054707) [92, 93]. Photodynamic therapy (PDT) is also under clinical trial for HS. A study of intralesional PDT in HS patients showed remission of disease in 5 out of 7 patients. However, PDT in other studies showed adverse outcomes too [94, 95]. Antibiotics with broad-spectrum coverage are also under clinical trials. Intravenous treatment with ertapenem decreases in Sartorius score from 49.5 to 19.0 while other study reported reduced disease severity and improved quality of life [96]. Steroids such as prednisone and triamcinolone acetonide have also shown some improvement in HS symptoms such as reduction in edema, erythema, and suppuration [97, 98].

Antidiabetic agents such as Liraglutide, a glucagon-like peptide-1 agonist [99] and metformin [100] have shown some efficacy in a HS patients, however, the exact mechanistic target of action of these drugs is still unknown. Other drugs targeting various signaling molecules such as Apremilast (PDE4 inhibitor), KT474 (IRAK4 inhibitor), LYS006 (LTA4 inhibitor), CFZ533 (anti-CD40 antibody), LY3041658 (antibody targeting ELR+CXC chemokines), Efalizumab (humanized monoclonal antibody to CD11a/ITGAL) and Spesolimab (IgG1 antibody against IL36R) are also in clinical trials of HS.

An extra cellular membrane component, AMP-001 (Allogeneic Micronized Amniotic Membrane Product) is also in clinical trials for the treatment of HS. Amniotic fluid is generally rich in collagen substrates, growth factors, amino acids, polyamines, lipids, carbohydrates, cytokines, extracellular matrix molecules like hyaluronic acid and fibronectin, cells, and various other chemicals, which are needed for tissue protection, repair, and regeneration. Patients treated with AMP-001 have indicated positive responses (https://clinicaltrials.gov/ct2/show/NCT04541550). The multiplicity of therapeutic agents with distinct molecular targets is a clear indication of undefined and complex pathogenesis of HS.

6. Conclusion

Several layers of dysregulated cellular and molecular signaling are known to be involved in HS pathogenesis, but the cause and effect relationship is not established yet. A major reason for lack of in-depth understanding of HS pathogenesis is the unavailability of suitable animal models that could recapitulate faithfully most of the disease symptoms

and unravel the molecular pathogenesis. Furthermore, mechanism-based critical evaluation of drug molecules also requires *in vitro* or/and *in vivo* animal models. Undoubtedly, these models will accelerate the screening and selection of highly potent drug candidates. In addition, these models will help in defining disease confounding pathways that are activated by various clinical comorbidities, environmental and chemical interactions, such as smoking, obesity, bacterial/fungal infection and ECM degradation and other inflammatory cues. Further, the molecular events that orchestrate various components of disease progression and recurrence of HS are needed to be uncovered, which will provide a basis for effective cure of this debilitating disease.

In summary, the successful treatment of HS may require many strategies to be employed as single strategy and/or in combination. Deconvolution of pathogenic communication between various cell types such as keratinocytes, immune cells, fibroblasts, and dermal components along with their interaction with the outer and inner microenvironment is the ultimate necessity to uncover the mechanism(s) underlying the development of sinus tracts and the recurrence of the disease. Genetic understanding of the racial disparity is another important area of investigation for HS in addition to various other inflammatory skin diseases. Some of these HS lesions have high chance to progress into SCCs, which needs to be investigated in terms of both defining molecular signatures as well as underpinning mechanism. Finally, defining overall underlying molecular mechanisms of disease progression could not only lead to more effective therapies, but will also provide prognostic tools to identify HS patients at high risk for development of aggressive and resistant disease.

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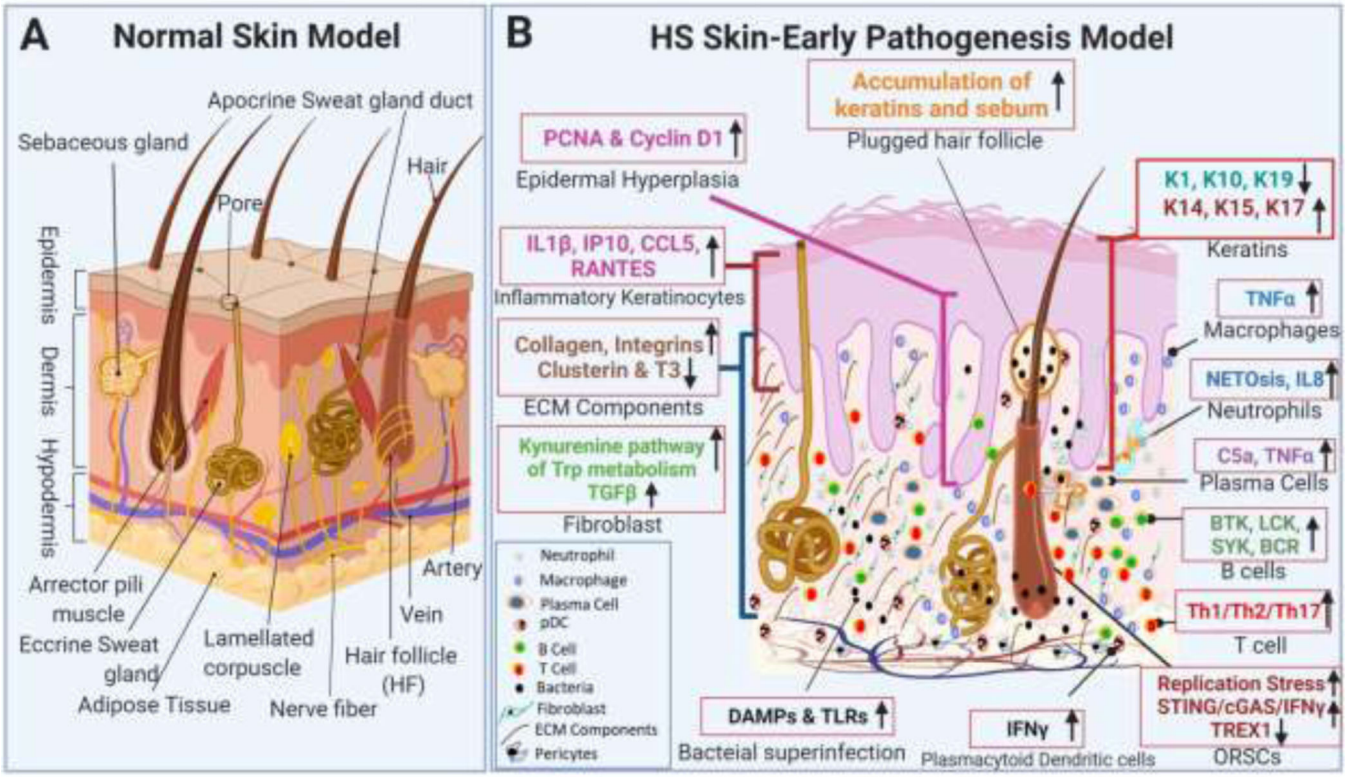

Figure-1:

Comparative description of skin phenotype in normal healthy and HS patients subjects. A. Normal skin; B. HS skin during early disease. Please note that as compared to normal skin, HS skin is hyperproliferative with intense infiltration of inflammatory cells, beginning of hair follicle clogging and disruption. Disease skin microenvironment is also unique with the release of multiple cytokines, ECM components and other clastogens. The localization of keratins that define skin keratinocyte types is also altered in HS Skin. This figure is created with BioRender.com.

Table 1:

Aberrant ECM signaling in various Diseases

ECM Components	Change expression/functions in pathogenesis	Reference
Collagen	CCL18 producing $CD163^{+}$cells (M2 macrophages) impact dermal fibroblast in promoting production of collagens (such as Col1A1, Col2A1, Col3A1) involving TGFβ and SMAD2/3 signaling	DOI:10.1111/bjd.16600 DOI: 10.1016/S0014-4835(02)00248-8 DOI: 10.4049/jimmunol.0903306 DOI: 10.1074/jbc.M100754200 DOI: 10.3181/00379727-232-2320406 DOI:10.1016/S1074-7613(00)80530-0 DOI: 10.1016/j.molimm.2011.09.006
	Cytokines IL4, IL13 and IL33 secreted by immune cells stimulates synthesis of ECM components. IL13 is important in differentiating fibroblast into myofibroblast, a key step in tissue fibrosis	
	Collagen peptides interact with inhibitory LAIR-1 receptors on immune cells to reduce their cytotoxic function associated with epidermal hyperplasia, bacterial infection or nociception	
Elastin	In fibrosis, elastin peptides activated fibroblast and augment cytokine production via ERK signaling	DOI: 10.1016/j.patbio.2011.10.006 DOI: 10.1016/s0014-5793(02)03057-0 DOI:10.3390/app11188732
	Elastin peptides act as chemotactic agents regulating tissue trafficking of macrophage and neutrophils	
	Elastin peptides induce ROS in immune cells and enhance elastase and MMPs	
	Low Elastin concentrations impact T cell proliferation and polarization	
Laminin	Laminin plays role in proliferation, migration and adhesion of immune cells	DOI:10.1016/j.it.2017.06.002 DOI:10.3389/fcell.2019.00068
	Laminin fragments/processed peptides act as DAMPs and alter expression of cytokines and MMPs	
Fibronectin	Fibronectin and its variants modulate T cells and TLR signaling	DOI: 10.1109/CSPA.2012.6194761 DOI:10.1371/journal.pone.0102974
	Fibronectin regulates secretion of cytokines/chemokines in fibroblasts	
ECM-1	ECM-1 secreted by Th2 immune cells affects Th17 responses	DOI: 10.4049/jimmunol.1502457.
	ECM-1 impacts TGFβ signaling	