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Contribution of Fibroblasts to Tunnel Formation and Inflammation In Hidradenitis Suppurativa/ Acne Inversa

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Abstract

The precise pathogenic mechanisms in the development, persistence and worsening of Hidradenitis Suppurativa (HS) remain ill-defined. This chronic inflammatory dermatosis displays a strong Th1 and Th17 inflammatory signature with elevated levels of TNF-α, IL-1β, IL-17 and IFNγ in lesional and perilesional tissue. HS significantly differs to other chronic inflammatory dermatoses due to the development of hypertrophic scarring and dermal tunnels. The development of scarring and tunnels suggests that fibroblastic stromal cells (including myofibroblasts, fibroblasts, pericytes etc.) may be involved in the development and progression of disease. Heterogeneous populations of fibroblasts have been identified in other inflammatory disorders and malignancy which contribute to inflammation and present novel therapeutic targets for fibrotic disorders. Findings in HS are consistent with these fibroblast subpopulations and may contribute to tunnel formation, aggressive squamous cell carcinoma and the phenotypic presentation of familial HS variants. We describe the existing knowledge regarding these mechanistic pathways and methods to confirm their involvement in the pathogenesis of HS.

Keywords

Hidradenitis Suppurativa; Acne Inversa; Pathogenesis; Fibroblasts; Scarring

1. Introduction:

The precise pathogenic mechanisms in the development, persistence and worsening of Hidradenitis Suppurativa (HS) remain ill-defined[1]. This chronic inflammatory dermatosis displays a strong Th1 and Th17 inflammatory signature with elevated levels of TNF-α, IL-1β, IL-17 and IFNγ in lesional and perilesional tissue[2]. HS significantly differs to other chronic inflammatory dermatose[3] due to the development of hypertrophic scarring and dermal tunnels[4]. The development of which suggest that fibroblastic stromal cells (including

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myofibroblasts, fibroblasts, pericytes etc.) may be involved in the development and progression of disease[5]. The recent investigations by Sanchez et al[5] experimentally demonstrate that biologically active peptides and inflammatory mediators from the extracellular matrix (ECM) engage in inflammatory crosstalk with keratinocytes in HS. This paper begins to lay the foundation for future investigations into the interaction between ECM, fibroblasts and keratinocytes in HS. Such insights may help explain why certain patients are prone to hypertrophic scarring, tunneling and tract formation, and the mechanisms underlying these presentations. This may also lead to the identification of novel therapeutic targets which overlap with pipeline drugs for fibrotic diseases[6]. A large body of literature exists regarding epidermal-stromal interactions in the setting of cutaneous melanoma[7] and other inflammatory disorders such as Rheumatoid Arthritis (RA)[8] and Inflammatory Bowel Disease (IBD)[9], however, investigations in inflammatory skin disease are limited. Our background knowledge in these conditions may help generate testable hypotheses regarding the mechanisms at play in inflammatory dermatoses including HS.

2. Mesenchymal Stromal Cells as a Heterogeneous Population:

Fibroblast populations in chronic inflammation and malignancy are heterogeneous. Fibroblasts are identified by their spindle shaped cellular morphology in combination with common mesenchymal markers such as vimentin[9–12] and develop from multiple sources including resident tissue stromal cells, bone marrow derived stromal cells, Epithelial Mesenchyme Transition (EMT) and Endothelial Mesenchyme Transition (endoMT) from epithelial and endothelial cells, respectively.[10,11] The source of these stromal cells can be identified through examination of specific cell markers (such as PDGFRα, PDGFRβ and Podoplanin)[9–12], however, no individual marker is known to be predictive of function. Transcriptomics and single cell RNA sequencing (scRNAseq) have recently been able identify and characterize subpopulations of stromal cells[9,11] and provide insights into their putative function in malignancy and inflammation. Factors including cellular origin, spatial location, microenvironment and degree of differentiation all contribute to the functional phenotype (i.e. matrix re-modelling, epithelial maintenance) of fibroblasts identified in these disorders[9–12]. This results in a heterogeneous milieu of fibroblasts which are proposed to be differentially dysregulated in different forms of aberrant wound healing, fibrosis, hypertrophic scarring, malignancy and metastases[9–12]. Common fibroblast subpopulations have been identified within chronic inflammatory conditions, chronic wound healing, malignancy and metastasis[9–12]. This indicates common pathways may be at play which are potential therapeutic targets in these various disorders.

3. The role of Fibroblasts in chronic inflammation and epithelial integrity:

Fibroblast dysregulation has been implicated in impaired wound healing[12], inflammatory disorders such as pyoderma gangrenosum[14] (associated with HS in the PASH and PAPASH syndromes)[15], and in the development of tertiary lymphoid follicles[12] in RA and IBD.[15] Dysregulation is proposed to involve priming signals in the stromal environment during acute inflammation (mediated by granulocytes) to epigenetically modulate fibroblasts, leading to expression of markers including α-SMA, S100A4, FAP-α[16]. Such activation is purported to result in epigenetic modifications[17] given the persistence of the activated

phenotype after isolation of cells and *in vitro* culture[12,15,17]. This activation leads to upregulation of ICAM-1, VCAM-1 CXCL13, CCN2, IL-6[18,19] as well as NLRP3 and Caspase-1 inflammasome activation leading to further IL-1β, IL-18 release, matrix metalloproteinase (MMP) production and release[9,10,15], and leucocyte recruitment[18,19] . MMPs are required for the activation of pro IL-1β, pro TNF-α, pro TGF-β as well as potentiating the action of IL-8[20]. In normal tissue, the presence of a second maturation and stabilization signal (including activation of the TNFRSF3 Pathway and RORγ pathway)[15] ensues, however, blockade of these signals leads to a disorganized collection of mixed inflammatory cells reminiscent of the mixed inflammation in established HS.

Bidirectional stromal-epithelial signaling via the Wnt pathway is integral to maintaining the epidermal stem cell compartment[13]. Dysregulation of this signaling leads to poor epidermal regeneration and is implicated in impaired wound healing and ulceration in Crohn's disease[9]. A specific subpopulation of fibroblasts, found adjacent to the involved epithelium, has been identified which mediates this bidirectional signaling via CD44[9–12,16], however, communication can occur without direct cell to cell contact[21] via microvesicles[18] or other not-yet-identified mechanisms. Upregulation of Wnt signaling has been shown to accelerate both fibrosis and re-epithelialization in animal and human models[22], with Wnt/B-Catenin signaling being suppressed in cutaneous wounds of diabetic patients[22,23], a common comorbidity in HS.

4. Fibroblast Like Stromal Cells in Malignancy and Metastases

In the setting of malignancy, dysregulated fibroblasts are known as cancer-associated fibroblasts (CAFs)[10,11,16,24,25]. CAFs are associated with increased tumor growth and metastatic potential as well as extra cellular matrix remodeling[10,11,16,24,25]. CAFs contribute to the pro-inflammatory nature of the tumor microenvironment[25] and remodeling of the ECM[11,16] . Bidirectional crosstalk with tumor cells has been shown to increase the metastatic potential of melanoma, breast, pancreatic and lung tumours,[11,16,24,25]. Stromal-derived IL-6 and TGF-β have been documented to suppress cell cycle progression in melanoma[27], controlling tumor spread in early stage disease. However, in the setting of malignancy with activated fibroblasts, the altered CAF secretome results in exposure of the tumor cells to growth factors and metabolites which promote tumor propagation[28]. CAFs have been shown to harbor immunomodulatory mechanisms with upregulation of production of cytokines and chemokines, including PDGF, vascular endothelial growth factor A (VEGFA), prostaglandin E2, IL-6, TNF, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), IL-8, hepatocyte growth factor (HGF), and CXCL12[28,29]. This inflammation results in an autocrine signaling capability in CAFs contributing to ongoing inflammation. Activated CAFs, in a similar fashion to other fibroblasts, produce multiple MMPs including MMP1–3, MMP9, and MMP13–14, as well as tissue inhibitors of metalloproteinases (TIMPs), which together result in ECM remodeling. In malignancy, this remodeling facilitates tumor invasion and metastasis[29] . Additionally, activated stromal cells can induce EMT and motility in malignant cells via CD44 signaling[16]. The cause of this aberrant activation is secondary to the pre-existing inflammatory milieu, including the local microenvironment, EMT and EndoEMT programs, as well as the influx of heterogeneous populations of mesenchymal cells primed for activation from bone marrow. Concurrently,

expression of CCN2 and production of miRNAs can activate stromal cells to a CAF phenotype[24,25], demonstrating the extensive cross talk in the setting of malignancy.

5. Mesenchymal Subpopulations Mediate Disparate Functional Pathways in Inflammation, Fibrosis and Fistula Formation in Inflammatory Bowel Disease

Dysregulated fibroblasts are implicated in the development of inflammation, fibrosis and fistula formation in IBD[9], several inflammatory characteristics of RA[12,15], and enhanced metastatic potential in breast carcinoma[11]. Specific subpopulations of fibroblasts are associated with the loss of epithelial integrity, ECM remodeling, angiogenesis and development of tertiary lymphoid structures[9,11,12,15]. PDFGRA+ cells with differentially elevated expression of DCN, LUM, VCAN, Col14A1, FBLN1, FBLN2, SMOC, LOX, LOX1 and CXCL14 display an ECM and EMT related transcriptomic signatures associated with ECM remodeling and stimulation of EMT in epidermal tissues[9,10,11,12,15]. PDFGRB- fibroblasts with differentially elevated expression of POSTN, BMP2, BMP5, WNT5A, WNT5B, SOX6, SCRG1, SOX9, SOX10, MFAP5 and CCN2 were described as enriched in inflammation[9,10,11,12,15], and associated with fibroblasts derived from epidermal tissues via EMT. Podoplanin + fibroblasts were identified as a subgrouping of PDFGRA+ fibroblasts with expression suggestive of an EndoMT origin[9,10,11,12,15]. This subset has been implicated in the development of tertiary lymphoid follicles in chronic inflammation including IBD and RA[9,12,15] .NR2F2 expressing fibroblasts with elevated expression of Notch3, Epas1, and COL18A1 have transcriptomic profiles suggestive of a pro-angiogenic profile with a subset of these cells also expressing high levels of cell cycle related genes[9,10,11,12,15]. In IBD, an increase proportion of PDGFRA+ cells are implicated in T cell recruitment and barrier dysfunction[9]. This subpopulation was significantly expanded in IBD patients compared with healthy controls[9]. PDFGRB- fibroblasts were decreased in IBD and this subpopulation was implicated in epithelial maintenance[9].

6. The Inflammatory Signature of Hidradenitis Suppurativa Suggests a Possible Contribution of Fibroblasts

Existing studies in HS demonstrate intriguing evidence of fibroblast-related pathways being activated in lesional tissue. Elevations in IL-1β, IL-6, IL-8, MMP2 and MMP9 as well as extensive matrix remodeling are core manifestations of HS[1,2,5]. IHC studies have identified co-localization of MMP2 to dermal fibroblasts[30] . The presence of isolated keratinocytes in the dermis is a longstanding phenomenon in HS and can be explained by EMT and the motility of keratinocyte derived MSCs which still partially express keratinocyte markers[30]. The Invasive Proliferative Gelatinous Mass (IPGM), found attached to the epithelium of the sinus tracts of HS, has been characterized as an active inflammatory component of the disease and comprised of Neutrophil Extracellular Traps (NETs)[31]. Such NETs develop through a process of NETosis which is stimulated by IL-8, IL-6, TNF-α[32]. NETs have been documented to stimulate EMT and EndoMT in other autoimmune diseases such as lupus nephritis and rheumatoid arthritis[33]. Microbiota such as porphyromonas sp., which are

associated with HS and colonize epithelialized dermal tunnels, are known triggers of NETosis[32,34]. The extensive tunnel formation in HS may be partially explained by PDFGRA + fibroblasts stimulating matrix remodeling and tunnel formation, whilst the epithelialization of dermal tunnels may be partially explained by the role of PDFGRB- fibroblasts in stimulating re-epithelialization as a form of aberrant wound healing. Such epithelialized tunnels may then perpetuate Th17-mediated keratinocyte feed forward inflammation, as well as stimulating fibroblasts to produce IL-6 and IL-8. This may partially explain the dramatic reduction in draining fistula counts with IL-23 blockade[35].

7. Stromal Cell MMP secretion linked to gamma secretase associated pathways:

Gamma secretase associated polymorphisms have been identified in a minority of patients with familial HS[36.] These polymorphisms involve three of the four subunits of the gamma secretase complex - Nicastrin, Presenilin 1 and the Presenilin enhancer[36]. The existing hypothesis is that gamma secretase polymorphisms alter Notch signaling which leads to hyperproliferative keratinocytes in the follicular infundibulum leading to follicular occlusion[1], however, the possibility of alterations in Notch signaling representing a generalizable inflammatory phenomenon (rather than a mechanistic pathway specific to HS) have not been experimentally tested[37]. Nicastrin (NCSTN) haploinsufficiency is shown to decrease expression of Interferon related genes in HEK293 cells[38], however, does not alter cytokine profiles of stimulated PBMCs[39]. An only recently appreciated aspect of the gamma secretase complex is its role in fibrosis[40–42]. Presenilin-1 is the proteolytic component of gamma secretase which is responsible for degradation of CD44 as well as other adhesion molecules such as N-cadherin[40] .Cao et al's Nicastrin knockdown model also revealed downregulated N-Cadherin and upregulation of CXCL14[38], which in addition to its immune surveillance properties, is an autocrine factor associated with activated fibroblasts[43]. Given the role of Nicastrin as the 'gatekeeper' of the catalytic activity of the gamma secretase complex[41,42], polymorphisms in Nicastrin leading to overactivity of gamma secretase can theoretically lead to profibrotic activity through upregulation of EMT and cellular motility[40–42]. Presenilin 1 also upregulates TGF-β activity, MMP secretion and the β catenin/Wnt pathway[40,44]. Upregulation of extracellular proteolysis would also explain the excessive fibrotic extensive matrix remodeling and significant scarring seen in Chinese HS patients with documented Nicastrin mutations[37], as opposed to the typical axillary-mammary inflammatory form of the disease[1].

8. Stromal Cell Contribution May Explain Aggressive Behaviour of SCC in HS

One of the most serious complications of long-term HS is the development of aggressive, metastatic squamous cell carcinoma[45–47]. Despite their well differentiated nature, these tumors rapidly metastasize and can be fatal. Suggested contributing factors include human papillomavirus infection[48] as well as the propensity for longstanding chronic wounds to develop SCCs[49]. Despite this well documented association between chronic non-healing wounds, the exact mechanisms remain unclear. Evidence from Epidermolysis Bullosa

(Recessive Dystrophic, Generalized Severe subtype)[47] implicates a unique dermal microenvironment (including elevated Wnt5A and TSP1 signaling along with a dense population of inflammatory cells and activated fibroblasts) in the development and rapid progression of cutaneous SCC, which are often fatal[47]. Additionally, gram negative flagellated bacteria may activate TLR5 in RDEB contributing to the pro-tumorogenic environment[47]. These same upregulated factors are identified in PDFGRB- fibroblasts in Crohn's disease, and are associated with epithelial maintenance[9]. This implies a potential common mechanism in the development of highly aggressive RDEB and other diseases including Crohn's disease and possibly HS.

9. Common mesenchymal pathways may explain the association of Pyoderma Gangrenosum/ IBD/ Arthritis and Neutrophilic Alopecias

Monogenic Autoinflammatory Syndromes manifest in both HS and other inflammatory disorders such as Pyoderma Gangrenosum and Inflammatory Arthropathies including the PASH and PAPASH syndromes[50]. HS also has a strong epidemiological association with IBD[1,51]. The coexistence of these conditions implies a possible degree of commonality in their pathogenesis. Dysregulated fibroblasts have been implicated in inflammatory arthropathies and play a significant role in impaired wound healing[19,22,23,52]. The pro-inflammatory actions of activated fibroblasts are NLRP3 and Caspase-1 inflammasome mediated[9,10,15], lending credence to the suggestion that they may be involved in the pathogenesis of PAPA and PASH syndromes, given the association of these syndromes with pathogenic sequence variants in these pathways[36]. The corollary of this is that other manifestations of these disorders (such as Pyoderma Gangrenosum) may also involve fibroblast dysregulation as a manifestation of aberrant wound healing. The hypothesis would include a role for the increase of PDFGRA+ fibroblasts due to the extensive degree of ECM remodeling and a decrease in PDGFRB- fibroblast which are responsible for epithelial integrity in a similar fashion to colonic ulceration in IBD[9]. Two other cutaneous conditions bear striking histological, clinical and immunological resemblance to HS, Dissecting Cellulitis of the Scalp and Complex Pilonidal Disease, and the involvement of fibroblasts in these disorders warrants further consideration.

10. IL-17, IL-1, CXCL14, JAK-STAT, Cadherin-11, CDK, miR-203, FRP2/ALX, podoplanin, CCN2 pathways are potential therapeutic targets of Fibroblasts in HS.

There is an urgent need for novel therapies in HS and therefore, identification of novel druggable targets is critical. The presence of distinct fibroblast subpopulations has been identified in lesional and perilesional HS tissue which mirror the expression markers (PDGFRA+, PDGFRA-, NR2F2, Podoplanin) seen in other inflammatory conditions such as Crohn's disease (Lu et al, unpublished data), although their functions in vivo remain to be established. A number of fibroblast-targeted therapies exist within the rheumatological and immunological therapeutic pipeline[53]. Along with IL-17, IL-1 and JAK-STAT blockade, (currently in Phase 2 clinical trials)[54], other druggable targets include IL-6R, Cadherin 11,

cyclin dependent kinases (CDK1, CDK2, CDK4, CDK6), SYK (reducing IL-6 production via the MAPK-PKC pathway), CXCL14, CCN2 as well as Formyl peptide receptor 2 (FRP2/ALX) as a upstream mediator of Stat 1, IL-6 and Podoplanin. One potential complication of note is the disparity between responses to therapy between joint-derived versus skin-derived fibroblasts[55] which is reflected in the imperfect efficacy correlation between skin and joint targets in psoriasis and psoriatic arthritis[56].

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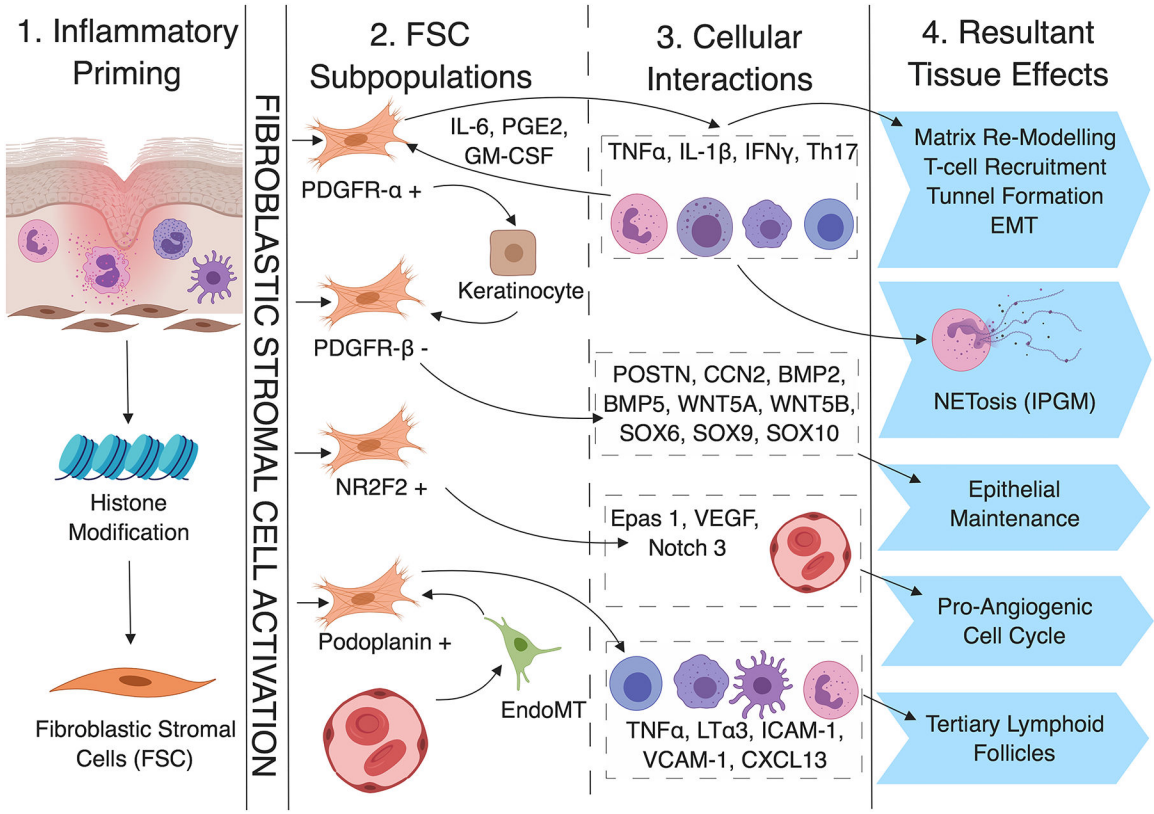

Figure 1:

Proposed Role for Fibroblasts in Tunnel Formation and Inflammation in Hidradenitis Suppurativa. Acute inflammation may act as a priming signal for the activation of fibroblasts through epigenetic mechanisms (1. Inflammatory Priming) leading to the emergence of four discrete subpopulations (2. FSC Subpopulations). Each subpopulation demonstrates specific functional characteristics via actions involving specific inflammatory mediators, transcription factors and cellular pathways (3. Cellular Interactions). Such interactions are associated with (and proposed to be mechanistic causative in) the development of tunnels, epithelialized tracts and fibrosis in HS (4. Resultant Tissue Effects).