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3D-SeboSkin Model for Human ex vivo Studies of Hidradenitis Suppurativa/ Acne Inversa

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Keywords
Hidradenitis suppurativa · Skin model · Ex vivo · 3D-SeboSkin

Abstract
Background: Hidradenitis suppurativa/acne inversa (HS) is a chronic, recurrent inflammatory skin disease. Its pivotal pathogenetic event is believed to be the occlusion of the hair follicle generating a perifollicular lympho-histiocytic inflammation. However, knowledge of the exact HS pathogenesis requires further research. ***Objective:*** To develop a human HS model applicable in preclinical research which could help to understand the pathophysiology of HS and to determine the action of therapeutic candidates. ***Methods:*** The 3D-SeboSkin technology was applied to maintain explants of involved and uninvolved skin of HS patients ex vivo for 3 days. Detection of differential expression of previously detected HS biomarkers was performed by immunohistochemistry in a group of female patients ($n = 9$, mean age 37.2 ± 8.4 years). ***Results:*** The application of the 3D-SeboSkin model preserved the structural integrity of lesional and perilesional HS skin ex vivo, as previously described for healthy skin. Moreover, the HS 3D-SeboSkin setting maintained the differential expression and pattern of several HS biomarkers (S100A9, KRT16, SERPINB3) in epidermal and dermal tissue and the appendages. ***Conclusion:*** We have validated HS 3D-SeboSkin as a reproducible, human model, which is appropriate for preclinical lesional and perilesional HS skin studies ex vivo.
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Introduction

Hidradenitis suppurativa/acne inversa (HS) is a chronic, recurring, and debilitating inflammatory skin disease of the hair follicle that usually presents after puberty with painful, deep abscesses and inflamed lesions in the apocrine gland-bearing areas of the body, most commonly at the axillae, inguinal, mammary, and anogenital regions (Dessauer definition) [1, 2]. Current epidemiological studies have reported a disease prevalence of 0.4% to a suggested maximum of 1% in Europe [3]. The pivotal pathogenetic event in HS is considered to be the occlusion

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of terminal hair follicles of the inverse skin areas leading to a perifollicular lympho-histiocytic inflammation. Significant efforts have been made to improve our understanding and management of the disease, but a major obstacle of studying HS pathogenesis more in depth was the lack of satisfactory preclinical models mimicking the complex phenotype of this skin disorder until recently, whereas the lately reported ones need further validation [4]. On the other hand, animal sacrifice in order to detect the effects of investigative compounds was a major reason for the recent restrictions of animal use in pharmaceutical and cosmetic industry [5]. Furthermore, HS is a solely human disease and animal skin is somehow different from human skin regarding their anatomy and physiology.

In a previous own work, we have developed 3D-SeboSkin, a model of maintenance of human skin ex vivo, which prevents the rapid degenerative events observed during maintenance of human skin in culture [6]. Moreover, we have performed whole genome profiling to identify dysregulated genes associated with HS pathology through the comparison of lesional, non-lesional, and healthy control skin [7]. Comparing lesional versus non-lesional as well as lesional versus control skin, 16 genes were identified, which further characterize HS from a molecular standpoint, and we have localized them in the skin compartments by immunohistochemistry. In the present work, we applied the 3D-SeboSkin model and successfully maintained lesional and perilesional HS skin ex vivo. Moreover, we have investigated the ex vivo protein expression of the 16 previously detected HS markers and found the localization and differential expression of calgranulin B, keratin 16, and serpin B3 to be identical with that of HS skin in vivo. Therefore, we propose the reported HS 3D-SeboSkin as a preclinical model for testing the effectiveness of potential compounds against HS.

Materials and Methods

Co-Culture Model

3D-SeboSkin, developed to maintain human skin in culture [6], has been adapted for the introduction of HS skin in a co-culture model.

Cells

SZ95 sebocytes [8] were cultured in Sebomed® basal medium (Biochrom, Berlin, Germany) supplemented with 10% fetal bovine serum, 50 μg/mL gentamycin, 10 ng/mL human epidermal growth factor (EGF), and 1 mM $CaCl_2$ at 37°C and 5% CO_2 until reaching subconfluence. Before the start of co-cultivation experiments, SZ95 sebocytes were resuspended in serum-free medium (Sebomed® basal medium supplemented with 0.1% bovine serum albumin, 50 μg/mL gentamycin, 10 ng/mL human EGF, 1.5 mM $CaCl_2$, 1.5×10^{-7}M linoleic acid and 10^{-6}M retinol). 200,000 SZ95 sebocytes were seeded in 24-well plates and left overnight to attach at 37°C and 5% CO_2. On the next day, the wells were washed twice with phosphate buffered saline without Ca^{2+} and Mg^{2+} (PBS) and treated with 400 μL serum-free medium for direct contact co-culture experiments, respectively.

Skin Specimens

Full-thickness skin specimens were obtained from 9 Caucasian female patients (aged 37.2 ± 8.4 years) with HS Hurley stage II–III during surgery after provision of written informed consent. The patients did not present any other inflammatory or endocrinological disorders, including diabetes and thyroiditis, and were not pretreated for HS. Perilesional skin is defined as adjacent to HS lesional skin at a distance of ≥5 cm from visible inflammation area. The study was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (EA4/016/07) and was conducted according to the Helsinki Declaration rules.

Co-Culture Experiments

After subcutaneous fat excision, skin specimens were cut into similar pieces with dimensions of 3–5 mm. HS skin explants were cultured using the 3D-SeboSkin model as previously described [6].

Histology

Native skin specimens and specimens maintained 3 days in culture were stained with hematoxylin and eosin and proceeded to histological examination, as previously described [6].

Immunohistochemistry

Immunohistochemistry was performed as previously described [7, 9]. The formalin-fixed paraffin-embedded samples were incubated with a mouse monoclonal antibody against KRT6 (KRT6/1702, #ab218438; dilution 1:50, pH = 9), rabbit monoclonal antibodies against MMP1 (EP1247Y, #ab52631; 1:100, pH = 9), GJB2 (EPR8036 (2), #ab181374; 1:200, pH = 6), PI3 (EPR5515, #ab151549, 1:100, pH = 9), MMP9 (EP1254, #ab76003; 1:800, pH = 6), S100A8 (EPR3554, #ab92331, 1:4,000, pH = 9), KRT16 (EP1615Y, #ab76416; 1:4,000, pH = 9), and rabbit polyclonal antibodies against Ki67 (#ab15580; 1:1,000), HBD2 (HBD2, #ab63982; 1:200, pH = 9), SERPINB4 (SERPINB4, #ab 197096, 1:4,000, pH = 6), SERPINB3 (SERPINB3, #ab154971, 1:2,000, pH = 6), SPRR3 (SPRR3, #ab 218131; 1:100, pH = 9), S100A9 (S100A9, #ab63818, 1:2,000, pH = 6), S100A7A(15) (NICE2, #ab133877; 1:100, pH = 6), TCN1 (TCN1, #ab202121; 1:2,000, pH = 6), TMPRSS11D (TMPRSS11D, #ab127031, 1:20, pH = 6) (all from Abcam, Cambridge, UK) at the individually mentioned conditions at room temperature in three steps of 30 min, 24 h, and 30 min, accordingly. All antibody concentrations were titrated in preliminary experiments and were applied in dilutions of exponential labeling density, enabling comparisons of the labeling density among specimens labeled with the same antibody. The antibodies were diluted with a background reducing antibody diluent (Agilent, Dako). Anti-rabbit immunoglobulins (Agilent, Dako) were used as secondary antibodies and the reaction was visualized by a diaminobenzidine visualization kit (REAL EnVision Detection System; Agilent). The procedure of staining was repeated twice for each case, each time individually evaluated. Staining analysis was performed by image J. All slides were examined randomly and evaluated using the same scale.

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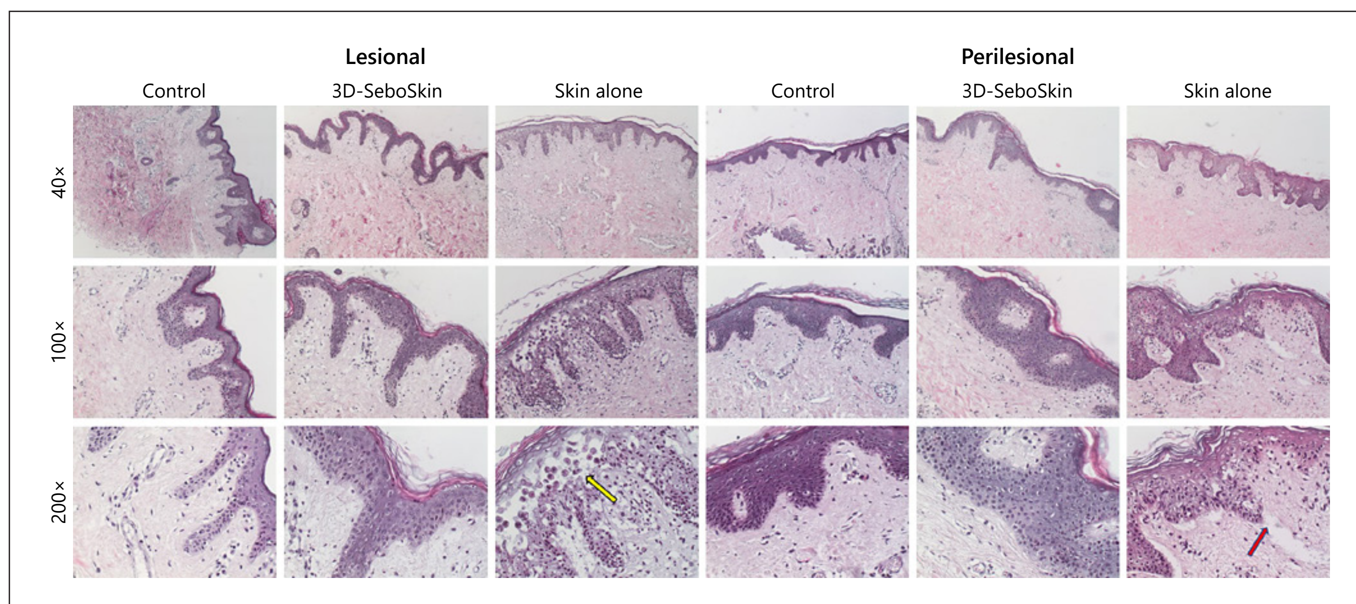

Fig. 1. Structural integrity of the HS skin epidermis could be better maintained by the HS 3D-SeboSkin model. HS skin was cultured with or without SZ95 sebocytes after 3 days in direct contact. Lesional skin and perilesional skin at time of surgery were regarded as control. Paranuclear vacuolization of basal and suprabasal keratinocytes (yellow arrow), separation of the epidermis from the dermis (red arrow). A representative set of pictures is presented (magnification, ×40, ×100, and ×200).

Statistics

GraphPad 6 was used for data analysis in this study. All results are presented as mean ± SEM. Shapiro-Wilk test was used to test the distribution of the data. For statistical significance, one-way ANOVA with Tukey post-hoc test was used. Differences of $p < 0.05$ were considered significant.

Results

Structural Epidermal Integrity of Lesional and Perilesional HS Skin Explants Is Maintained in the 3D-SeboSkin Model

In this experiment, the lesional and perilesional skin of nine patients with hidradenitis suppurativa was co-cultured with and without human SZ95 sebocyte monolayers [8], as previously described for healthy skin [6]. After 3 days of skin culture ex vivo without co-culture with SZ95 sebocyte monolayers, the epidermal morphology was disintegrated and the basement membrane exhibited prominent signs of degeneration as shown by hematoxylin/eosin staining. The cells were detached (Fig. 1). Disintegration characteristics were more prominent in lesional than in perilesional skin. In contrast, the skin maintained in co-culture with SZ95 sebocytes (3D-SeboSkin) retained normal histomorphological characteristics regarding the epidermal structure, the integrity of the basement membrane, and adhesion between epidermal cells and epidermis to dermis (Fig. 1). These results indicate that application of HS 3D-SeboSkin, namely maintenance of HS lesional and perilesional skin in direct contact with SZ95 sebocyte mololayer cultures, can preserve HS skin integrity, as previously described for healthy skin [6].

Evaluation of Epidermal Cell Vitality in HS 3D-SeboSkin Model

Co-culture of HS lesional ($n = 9$) and perilesional ($n = 9$) skin explants with SZ95 sebocytes for 3 days in direct contact was assessed with Ki67 labeling to determine basal and suprabasal layer keratinocyte vitality and regeneration ability (Fig. 2a). Lesional skin explants exhibited 82.8 ± 6.3% Ki67-positive basal/suprabasal epidermal keratinocytes (mean ± SEM); perilesional skin explants presented 47.0 ± 7.8% Ki67-positive cells on day 0 (immediately after surgery) (Fig. 2b, c). Ki67-positive cells in lesional skin explants decreased significantly after 3 days to 7.7 ± 1.1% without SZ95 sebocyte co-culture ($p < 0.0001$) and to 47.2 ± 5.5% in the presence of SZ95 sebocytes ($p < 0.001$), respectively (Fig. 2a, b). Simultaneously, Ki67-positive cells in perilesional skin explants decreased sig-

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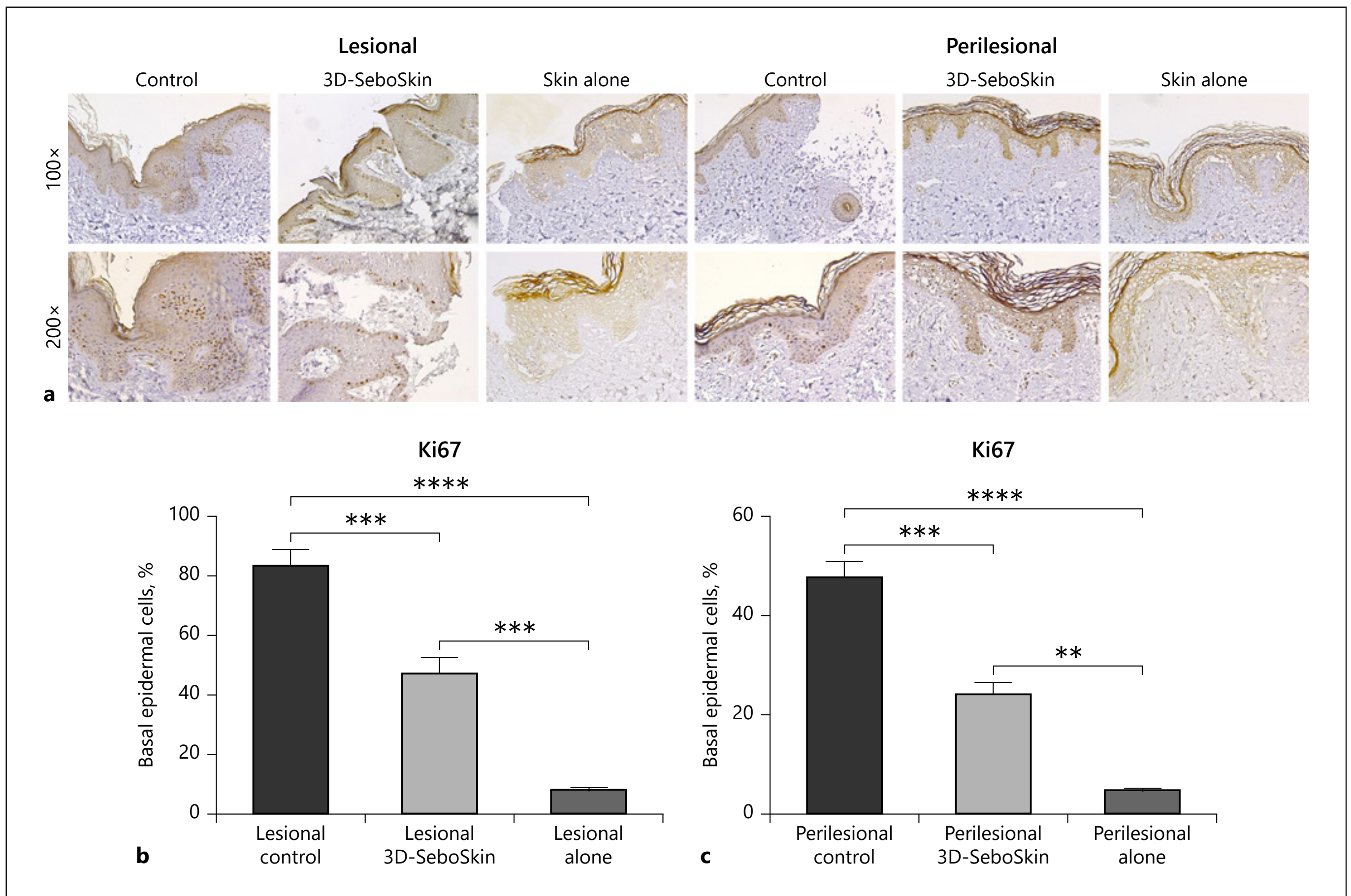

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Fig. 2. SZ95 sebocytes maintained Ki67 expression of basal epidermal cells in HS lesional and perilesional skin. Immunohistochemistry with antibodies raised against Ki67 before and after 3 days of direct contact coculture without and with SZ95 sebocytes in direct contact (**a**). Statistical analysis revealed a significantly higher conservation of the percentage of Ki67-positive epidermal cells in lesional (**b**) and perilesional (**c**) skin explants after coculture in direct contact with SZ95 sebocytes, in comparison with the cultured alone skins. A representative set of pictures is presented (magnification, ×100 and ×200). Staining analysis was performed by image J. ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

nificantly after 3 days to 4.4 ± 0.8% ($p < 0.0001$) without co-culture and to 23.6 ± 3.3% in the presence of SZ95 sebocytes ($p < 0.001$), respectively (Fig. 2a, c). Co-culture with SZ95 sebocytes resulted in a significantly higher percentage of Ki67-positive keratinocytes after 3 days of ex vivo skin maintenance compared to lesional ($p < 0.001$) and perilesional ($p < 0.01$) skin explants maintained without SZ95 sebocytes (Fig. 2b, c).

HS 3D-SeboSkin Setting Maintained the Differential Expression and Pattern of HS Tissue Markers in the Epidermis and the Appendages

Preliminary experiments with all antibodies tested have led to a selection of calgranulin B (S100A9), anti-keratin 16 (KRT16), and serpin B3 (SERPINB3) antibodies for further experiments. Immunohistochemical studies in HS skin explants were performed immediately after surgery and after ex vivo maintenance. S100A9 was present in follicular keratinocytes of the epithelial root sheath and epidermal keratinocytes of the stratum granulosum (Fig. 3a), KRT16 expression was detected in follicular keratinocytes of the external root sheath and epidermal keratinocytes of the stratum basale/spinosum (Fig. 3b), and SERPINB3 was expressed in follicular keratinocytes of the internal root sheath and epidermal keratinocytes of the stratum granulosum/corneum (Fig. 3c) in HS lesional and perilesional skin. After the 3-day maintenance in the 3D-SeboSkin culture, HS lesional and perilesional skin retained the localization and levels of S100A9, KRT16, and SERPINB3 expression. In contrast, S100A9,

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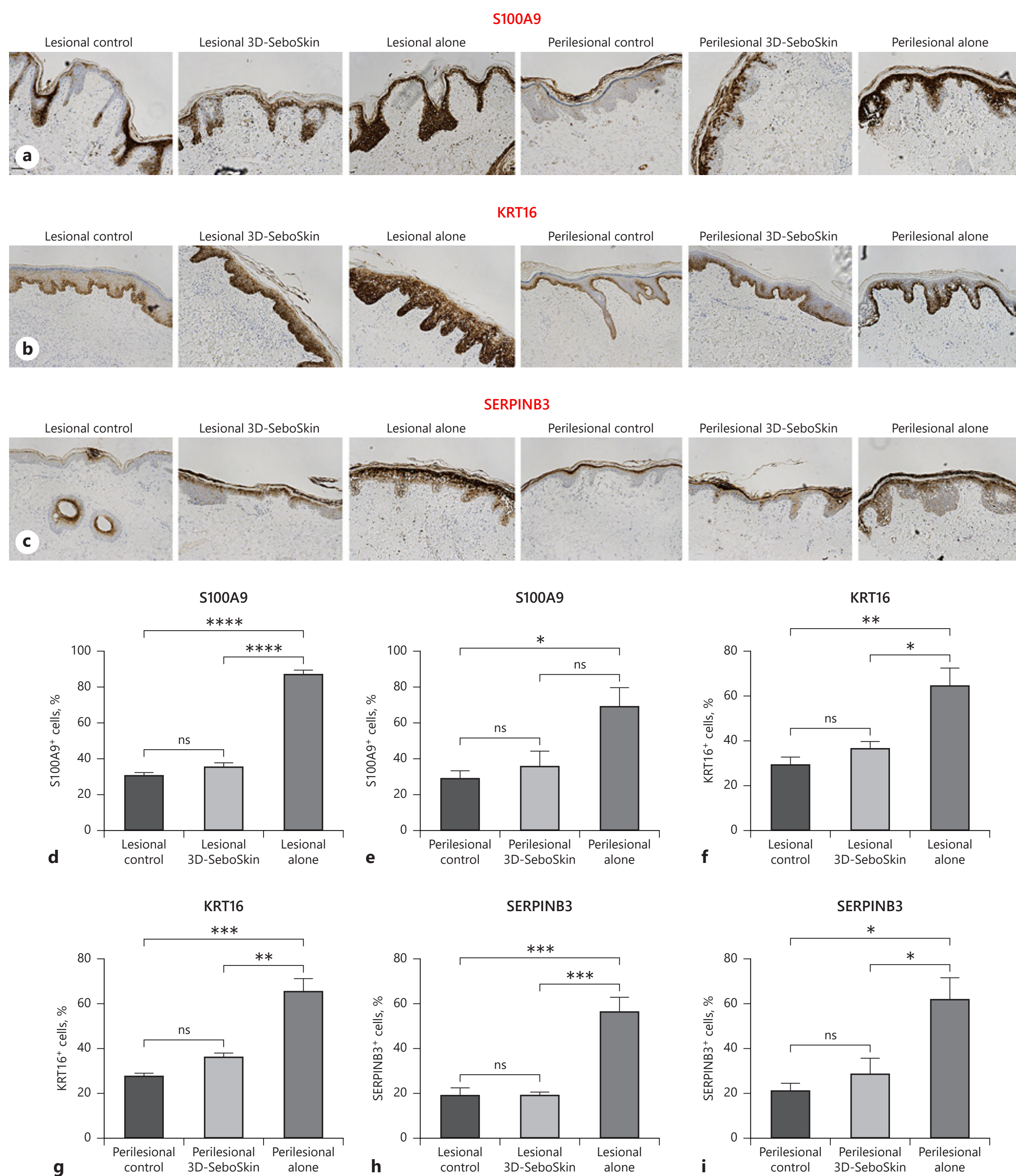

Fig. 3. Co-culture of HS skin explants (lesional skin, perilesional skin) with SZ95 sebocytes maintained the expression of S100A9, KRT16, and SERPINB3. Immunohistochemistry with antibodies raised against S100A9 (**a**), KRT16 (**b**), and SERPINB3 (**c**) before and after 3 days of coculture with and without SZ95 sebocytes in direct contact. Lesional skin and perilesional skin at time of surgery were regarded as control. A representative set of pictures is presented (magnification, ×100). S100A9 (**d**, **e**), KRT16 (**f**, **g**), and SERPINB3 (**h**, **i**) staining analysis of the relationship between control, skin cocultured with sebocytes, and skin cultured alone in 9 samples. A representative set of pictures is presented (bar 100 µm). Staining analysis was performed by image J. Results are presented as mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. ns, non-significant.

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KRT16, and SERPINB3 expression levels of the skin cultured alone were much higher than both in control skin and the HS 3D-SeboSkin (Fig. 3a–c).

To specify, in lesional HS skin, the expression of S100A9 in explants cultured alone was significantly higher than in control skin ($p < 0.0001$) and HS 3D-SeboSkin ($p < 0.0001$) (Fig. 3d). Similar results were assessed for KRT16 (control skin, $p < 0.01$; HS 3D-SeboSkin, $p < 0.05$) and SERPINB3 (control skin, $p < 0.001$; HS 3D-SeboSkin $p < 0.001$) (Fig. 3f, h). In contrast, S100A9, KRT16, and SERPINB3 (Fig. 3d, f, h) expression intensities in HS 3D-SeboSkin were equivalent to the expression in control skin.

In perilesional HS skin, the expression of S100A9 ($p < 0.05$), KRT16 ($p < 0.001$), and SERPINB3 ($p < 0.05$) (Fig. 3e, g, i) in cultured explants was higher than in control skin; however, the differences were smaller than those of lesional HS skin. A possible reason could be the lower inflammatory level of perilesional than lesional skin and its associated lower disintegration potential. Consequently, expression of S100A9, KRT16, and SERPINB3 did not differ between control skin and perilesional skin in 3D-SeboSkin (ns; Fig. 3e, g, i).

Discussion

Efforts for the development of adequate models for human skin diseases have mostly failed due to the inability of single cell cultures and skin equivalents to become "ill" in a similar manner and, therefore, match the complex human skin disease anatomy and biology as closely as possible.

In this study, we developed a human HS 3D-SeboSkin model based on our previous work on a viable three-dimensional healthy skin model [6]. This 3D model might devote to the comprehension of HS pathophysiology and the determination of novel therapeutic candidates. Indeed, the HS 3D-SeboSkin resulted in overall improved structural integrity of the lesional and perilesional skin, preserved the proliferating epidermal basal layer, and maintained the differential expression and pattern of the HS skin markers S100A9, KRT16, and SERPINB3 in the epidermis and the appendages [7].

HS 3D-SeboSkin represents, together with other ex vivo human skin models currently reported [10, 11], HS skin-like human models, whereas HS 3D-SeboSkin seems to overcome, for a period of time, the problem of rapid skin disintegration occurring in culture. In addition to the human ex vivo models reviewed by Zouboulis [4], monolayer cell cultures and a mouse model have been used to study the pathogenetic role of nicastrin mutations in HS. Ferri et al. [12] analyzed the effect of photobiomodulation on IL1β expression in the immortalized human keratinocyte cell line HaCaT using a wild-type line and a NCSTN knockout cell model mimicking genetic-driven HS. Yang et al. [13] generated a keratin 5-Cre-driven epidermis-specific NCSTN conditional knockout mutant in mice. The advantage of the HS 3D-SeboSkin model over the model by Vossen et al. [11] is its capacity to maintain an intact HS skin structure ex vivo for time periods longer than 24 h. Compared to healthy skin explants [6], ex vivo maintenance of HS skin explants, especially those of lesional skin, appears to be more complicated. This might be due to the inflammatory condition of lesional HS skin and its probable more prone status to apoptosis than healthy skin. On the other hand, it is interesting that SZ95 sebocytes can function as a homeostatic feeder not only for healthy skin but also for inflamed, diseased human skin, like HS lesional skin. Therefore, we assume that SZ95 sebocytes provide the essential factors to sustain skin explant vitality independently of its health condition. Interestingly Kamp et al. [14] have reported that sebaceous gland number and volume are significantly reduced in uninvolved hair follicles from patients with HS indicating that human sebocytes may contribute to or be affected by the inflammatory process induced in the involved hair follicles. In contrast, apocrine sweat glands are bystanders in HS-induced follicular inflammation [15]. Taking the results of HS skin morphology and the basal keratinocyte proliferation marker Ki67, we can conclude that through using the HS 3D-SeboSkin model, the structural integrity and epidermal vitality of the skin could be better maintained in comparison with the HS skin explants maintained alone in culture. This fact was also confirmed by the similar expression of S100A9, KRT16, and SERPINB3, which are characteristic HS skin markers at the protein level [7], in both lesional and perilesional skin in the HS 3D-SeboSkin model when compared with control skin immediately after surgery. The distinct expression levels of S100A9, KRT16, and SERPINB3 in lesional and perilesional skin, maintained without SZ95 cells, also indicates the superiority of the HS 3D-SeboSkin model. S100A9 is one of the representative antimicrobial peptides, which is upregulated in grouped skin cells in inflammatory skin diseases indicating cell cycle progression and differentiation [16, 17]. KRT6/16/17 has been recognized in recent studies as key early barrier alarmin upon skin injury, providing a rapid and specific innate immune response against danger signals [18]. At last, SERPINB3 is involved in the pathogenesis of inflammatory skin diseases, such as psoriasis and atopic dermatitis. In the latter, SERPINB3 expression is detected in the horny layer of skin

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lesions and the level of expression correlates with disease severity returning to baseline after successful treatment [19]. In keratinocyte studies in vitro overexpression of SERPINB3 was reported to protect against ultraviolet and gamma radiation as well as tumor necrosis factor-α-induced cell death [20, 21]. Overall, human SERPINB3 contributes to the cutaneous inflammatory response during the pathogenesis of chronic skin diseases.

In conclusion, we could validate 3D-SeboSkin as an adequate preclinical HS model, which has a series of advantages towards other research models currently applied. Its major advantage is the arrangement of the cells in a physiologic 3D architecture, thus facilitating the communication and interaction of different cell types with each other and the surrounding matrix. Although the model has its limitations, the detected conservation of skin architecture of both lesional and perilesional skin and the expression of HS biomarkers associated with inflammation makes the model eligible for the detection of beneficial or hazardous effects of various compounds planned to be applied topically or systemically for HS treatment.

Key Message

We present the application of 3D-SeboSkin, as a reproducible, human ex vivo model for preclinical studies on hidradenitis suppurativa.

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Statement of Ethics

Full-thickness skin specimens were obtained from 9 Caucasian female patients after provision of written informed consent. The study was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (EA4/016/07) and was conducted according to the Helsinki Declaration rules.

Conflict of Interest

The authors declare no conflicting interests. C.C.Z. is owner of an international patent on the immortalized human sebaceous gland cell line SZ95 (WO0046353).

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Author Contributions

X.H. performed the research, analyzed the data, and drafted the manuscript. A.K. and A.M.H. provided essential reagents and tools and participated at the experiments. G.N. had an active role in the establishment of the HS 3D-Seboskin model. O.B. played an essential role in performing immunohistochemistry. C.C.Z. developed the research concept, designed the study, supervised the research, and drafted the manuscript. All authors contributed to the last version of the manuscript.

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