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SHORT COMMUNICATION

Increased Expression of Integrin α6β4 in the Basement Membrane Zone Lining the Sebaceous Glands in Hidradenitis Suppurativa

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Hidradenitis suppurativa (HS) is an inflammatory skin disease characterized by painful nodules, abscesses and sinus tracts. The disease is located primarily in the apocrine gland-bearing skin, including the armpits and groins (1). Previous studies have shown that follicular occlusion is present in the majority of patients at an early stage of the disease (2–5); however, the driving mechanism behind this follicular occlusion is unknown. Recently, diminished periodic acid-Schiff (PAS) staining was found in the basement membrane zone (BMZ) of the sebofollicular junction (SFJ) at the folliculopilosebaceous units (FPSU) in perilesional HS skin (6). The authors suggest that the PAS-negative gaps represent primary defects in the BMZ, leading to fragility of the hair follicle. Diminished expression in one of the glycoproteins in the BMZ of the SFJ might explain these PAS-negative gaps; however, there was no staining for specific glycoproteins in this study. Therefore, we investigated the expression of the most important BMZ components, including type XVII collagen, type VII collagen, laminin-332, and integrin α6β4, of the follicular epidermis relative to the interfollicular epidermis in HS and compared the expression ratio with that of healthy controls.

MATERIALS AND METHODS

Skin samples were obtained from perilesional skin of patients with HS who underwent surgery ($n = 17$). Biopsies 4-mm thick were obtained from axillary skin of 8 healthy volunteers. The study was ethically approved by the local review board. PAS, and immunofluorescence (IF) staining for type XVII collagen, type VII collagen, laminin 332, integrin α6 and β4 were performed on all skin samples (for complete details see Appendix S1[1]). Staining intensities were measured at 5 segments of the FPSU: (*i*) the interfollicular epidermis (IFE); (*ii*) the superior segment of the hair follicle; (*iii*) the inferior segment of the hair follicle; (*iv*) the sebofollicular junction (SFJ); and (*v*) the sebaceous gland. The superior segment was defined as the part of the hair follicle extending from the IFE to the SFJ, the inferior segment as the part extending from the SFJ to the bulb. The SFJ was defined as the transition zone from the hair follicle to the sebaceous gland.

The intensity of the stainings at the aforementioned individual segments were analysed using Image J software. The ratio of individual segments to the IFE was calculated for both the PAS and IF stainings, with the IFE serving as an internal control for each skin sample. A Mann-Whitney *U* test was used to compare the differences in these ratios between patients and controls.

RESULTS

Skin biopsies of 10 patients and 2 controls were excluded due to the lack of an associated sebaceous gland. In total, biopsies of 7 HS patients and 6 controls were studied.

The IFE showed a continuous and regular PAS staining pattern in all biopsies with a mean intensity of 143.8 pixels (standard deviation [SD] 11.6) in controls

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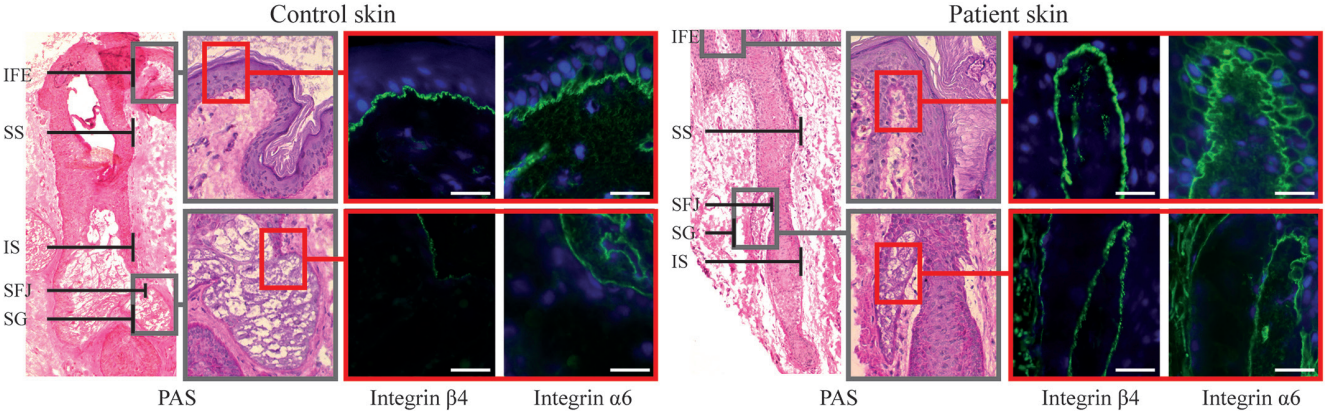

Fig. 1. Periodic acid–Schiff (PAS) and immunofluorescence (IF) staining of the interfollicular epidermis (IFE) and sebofollicular junction/sebaceous gland (SFJ/SG) in control and patient skin. There were no differences in the intensity of the PAS staining between the IFE and the SFJ/SG in both controls and patients. The additive staining intensity of integrins α6/β4 in the SG (*lower panel*) is higher in patient than in control skin. Scale bar = 20 μm. SS: superior segment.

and 150.0 pixels (SD 10.5) in patients. Therefore, the IFE served as a suitable internal control. There were no statistically significant differences between the ratios of the mean intensity of the PAS staining at the individual segments of the FPSU to the IFE in patients and controls (Figs 1 and 2).

For type VII collagen, type XVII collagen, and laminin 332 staining, no statistically significant differences were found between patients and controls in the ratios of the mean staining intensity at the individual FPSU segments to the IFE.

For integrin β4 and α6 staining, the mean intensity of integrin β4 at the sebaceous gland declined compared with the IFE in both patients and controls (Figs 1 and 2). The ratio of the mean intensity of integrin β4 at the sebaceous gland to the IFE was significantly higher in patients (0.41) compared with controls (0.14) ($p = 0.004$). This implies that integrin β4 expression at the sebaceous gland was relatively higher in patients. IF staining for integrin α6 also revealed a significantly ($p = 0.011$) higher level of expression at the sebaceous gland in HS compared with controls (Figs 1 and 2). It is plausible that the expression patterns of integrin α6 and β4 followed the same pattern, since they are dimerized in the integrin α6β4-complex. The relative expression of integrin α6β4 was not altered at the remaining FPSU segments in HS compared with controls.

DISCUSSION

This study demonstrates a relative upregulation of integrin α6β4 along the BMZ of sebaceous glands in HS patients.

A relatively large number of HS skin samples lacked an associated sebaceous gland in this study (58.8% (10/17) vs. 25.0% [2/8] in controls). This is in accordance with the findings of Kamp et al. (2), that sebaceous glands are frequently lacking or have a diminished volume in perilesional HS skin. In contrast to Danby et al. (6), reduced PAS positivity at the SFJ in HS was not observed, neither did we find any differences in PAS positivity within the remaining hair follicle segments.

One may speculate about the cause and consequences of integrin α6β4 upregulation in HS. Integrins are a family of heterodimeric glycosylated transmembrane receptors. They come primarily to expression in organs lined with stratified epithelium, such as the skin and lungs. In skin, the β4 integrins are primarily found in the BMZ. In addition to their significant adhesive function, integrins are important signalling molecules that have bidirectional actions. They show affinity with several extracellular proteins and are therefore involved in a variety of pathological processes, including oncogenesis, immune responses and inflammatory reactions (3, 4).

Upregulation of integrins α6β4, as found in the current study, was also described in bacterial-infected pulmonary tissue (5). Similar to lung tissue, changes in the bacterial community may be responsible for the integrin α6β4 upregulation we found in patients with HS (5). From this viewpoint, integrins may function as pattern-recognition receptors (PRRs), which, upon interaction with bacteria, induce cellular responses that activate the innate immune response (3). Also in Crohn's disease, which is presumed to have a pathogenesis similar to HS, integrins are thought to contribute to the aberrant immune response (7, 8). Moreover, anti-α4-integrins have shown to be effective in the treatment of Crohn's disease (8). The role of bacteria in the pathogenesis of HS is a topic of ongoing investigation (9). However, in addition to the possible role in integrin upregulation, alterations in the skin's microbioma may also explain why HS is mainly localized in the body folds, as these relatively moist areas harbour a different bacterial community from that found in other areas of the body (10, 11).

Finally, increased expression of α6β4 may also contribute to the development of squamous cell carcinoma (SCC), which is a well-known complication of HS (12, 13). In fact, mice with aberrant α6β4 expression showed a greater infiltration of immunosuppressive cells during tumour promotion, a phenomenon that may contribute to the susceptibility of SCC formation (13).

In conclusion, this study demonstrates upregulation of integrin α6β4 in sebaceous glands of patients with HS. This upregulation could result from alterations in

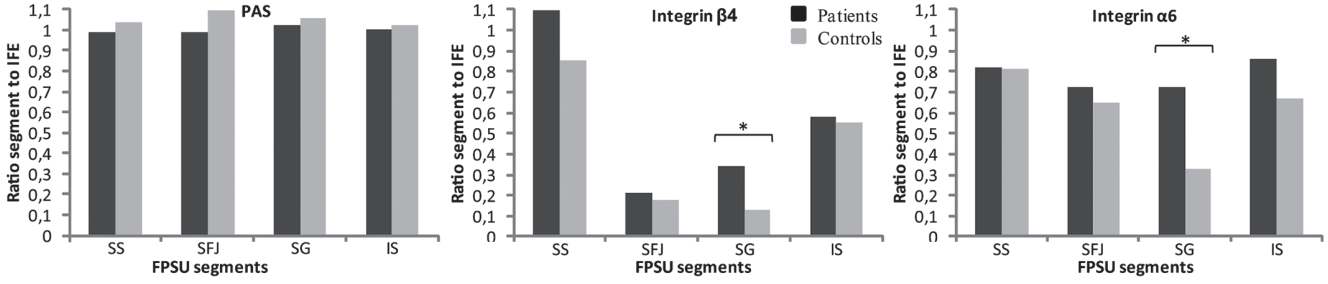

Fig. 2. Ratio of periodic acid–Schiff (PAS) and integrin α6β4 staining in various folliculopilosebaceous (FPSU) segments compared with the interfollicular epidermis (IFE) in patients with hidradenitis suppurativa ($n = 7$) and in 6 healthy controls. The bars represent the ratio of the mean PAS and integrin α6β4 staining intensities of the individually assessed FPSU segments to the IFE increased α6β4 expression of integrins β4 and α6 in patients' sebaceous glands (SG). SS: superior segment; SFJ: sebofollicular junction; IS: inferior segment. (*$p = 0.004/0.011$).

the skin microbioma and may contribute to the inflammatory reaction seen in HS as well as to the increased risk of SCC development in HS. Characterization of the skin microbioma in greater detail could provide further insight into the role of bacteria in HS and may provide a rationale for specific antibiotic treatments. Integrin α6β4 could be a putative treatment target for HS in the future.

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