Letter to the Editor

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Innate Immunity Protein Markers Are Significantly Elevated in Hidradenitis Suppurativa Skin Than in Psoriasis Vulgaris

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Dear Editor,

Hidradenitis suppurativa (HS) and psoriasis share pathophysiology characterized by the dysregulation of keratinocytes, upregulation of tumor necrosis factor (TNF) and interleukin (IL)-1 signaling, and hyperactivation of the T helper (Th)17 and IL-12/IL-23 axis. However, the efficacy of psoriasis-approved biologics, such as TNF inhibitors and IL-17A inhibitors in HS, was not as high as that in psoriasis, implying that HS had a more complex pathophysiology.[1,2] This study aimed to investigate the differences in expression patterns of shared inflammatory markers in HS and psoriasis.

We compared the mRNA and protein expressions of inflammatory cytokines and chemokines as well as the damage associated molecular patterns (DAMPs) in the skin of patients with HS to those of patients with psoriasis. Untreated moderate-to-severe HS (n=5, Hurley stage 2–3), moderate-to-severe psoriasis (n=5, Psoriasis Area and Severity Index score ≥7), and healthy normal controls (n=5) were enrolled in the study. The mRNA and protein expressions were analyzed by RT-qPCR and immunofluorescence staining according to the previously published protocols[3] (Supplementary Tables 1 and 2, only online), and fluorescence intensity was scored by three trained researchers independently. Ethical approval was obtained from the ethics committee of CHA Bundang Medical Center (IRB no. 2020-01-033).

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As shown in Fig. 1, IL-17C, IL-17A, CCL20, S100A7, S100A8, IL-36α, and DEFB4, which encodes human beta-defensin 2 (hBD2) were all significantly elevated in the lesional skin of both HS and psoriasis groups compared to the normal group. Although IL-17C was highly expressed in both epidermis and dermis of HS and psoriasis skin in the immunofluorescence staining, the mRNA levels of IL-17C were more elevated in psoriasis compared to HS (Fig. 1A). IL-17A was localized mainly in the dermis of both HS and psoriasis skin samples, and the mRNA levels of IL-17A were significantly elevated in lesional skins while psoriasis samples showed more significant elevation compared to HS (Fig. 1B). CCL20 staining had a higher intensity in epidermis than in dermis in both HS and psoriasis groups, and the mRNA expression of CCL20 showed no significant difference between the two groups (Fig. 1C). S100A7, S100A8, IL-36α, and hBD2, the molecules that are known to be produced mainly in the epidermal area, were highly expressed in the epidermis of HS and psoriasis skin in immunofluorescence staining. Specifically, the mRNA levels of S100A7, S100A8, and DEFB4 showed higher elevation in HS compared to those of psoriasis (Fig. 1D-G).

Taken together, IL-17C and IL-17A, which are known to be key pathogenic cytokines in psoriasis, were upregulated in HS skin compared to the normal control, while the gene expression in HS was significantly lower than that in psoriasis, which was in line with previous studies. Navrazhina, et al.[4] compared the inflammatory protein biomarkers of HS and psoriasis skin, and found that IL-17C and IL-17A showed upregulation in psoriasis compared to HS. In contrast, the expressions of the antimicrobial peptides, S100 protein family and hBD2, were significantly higher in the HS skin samples than in the psoriasis samples. S100 protein family, S100A7 and S100A8, are DAMPs that can exhibit antibacterial activity and modulate cell migration, invasion, and differentiation.[5] Similar to our findings, Zouboulis, et al.[6] performed whole transcriptome profiling of HS

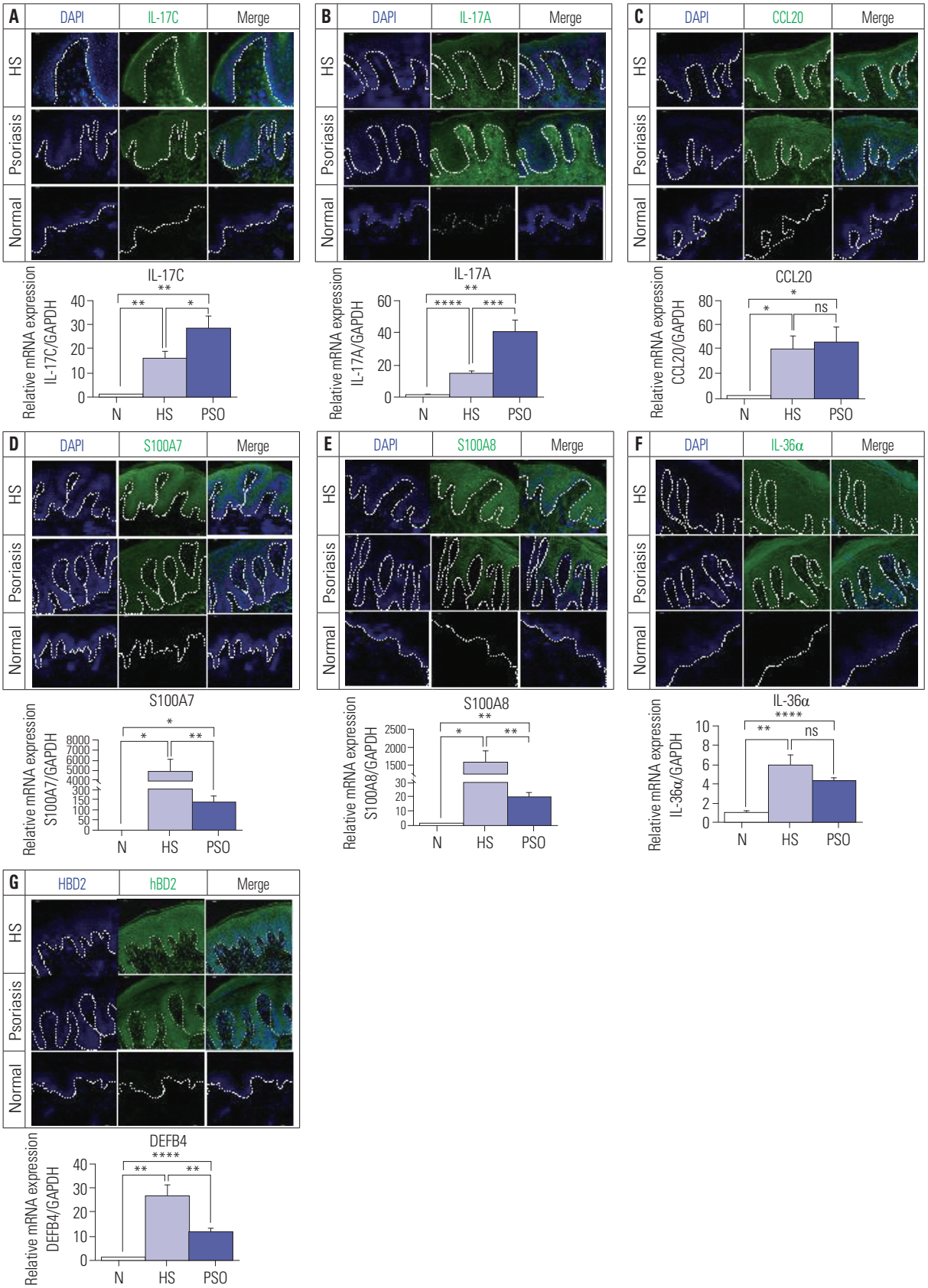

Fig. 1. Localization of cytokines and chemokines by immunofluorescence staining and quantification of mRNA levels relative to GAPDH expression. Proteins and their relative mRNA expressions of (A) interleukin (IL)-17C, (B) IL-17A, (C) CCL20, (D) S100A7, (E) S100A8, (F) IL-36α, and (G) hBD2 were significantly elevated (using unpaired t-test) in the lesional skin of hidradenitis suppurativa (HS) and psoriasis compared to that of normal controls. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. HS, hidradenitis suppurativa; N, normal; PSO, psoriasis.

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and demonstrated that S100A7, S100A8, S100A9, and S100S12 were dysregulated in HS. Previous studies also reported consistent overexpression of antimicrobial peptide hBD2 encoded by DEFB4 in HS and psoriasis,[3,5] and our study revealed that hBD2 expression was significantly higher in HS than in psoriasis. The upregulation of S100 proteins and hBD2 indicates functional dysregulation of keratinocytes in HS, which is possibly caused by altered skin bacterial flora. The unique features of HS skin microbiomes may play a crucial role in the stimulation of antimicrobial peptides and epidermal cytokines, resulting in skin inflammation.[2] Therefore, in the pathogenesis of HS, compared to psoriasis, innate immune response to pathogen invasion and abnormal keratinization seem to play important roles, along with the IL-17 pathway. According to the results of the present study, the treatment response of IL-17 inhibitors in HS appears to be not as effective as that of psoriasis.[7,8]

In summary, our study indicates that the role of shared pathophysiology might be different in HS and psoriasis. However, this study had a small sample size, and the locations of skin biopsy were not matched for each group. Due to these limitations, significant difference in the expressions of CCL20 and IL-36α may not have been detected. Lastly, due to the differences in disease severity scoring systems, it was difficult to directly compare the two disease groups. Moreover, the examination of tendrils and cysts in HS was difficult using punch biopsy samples, and a follow-up study using excision samples to compare the expression patterns of tendrils and cysts in the dermis to the epidermis is currently in progress. Prospective studies are required to further understand the pathophysiology of HS.

AUTHOR CONTRIBUTIONS

Conceptualization: Hee Jung Lee. Data curation: Sujin Moon. Formal analysis: Sujin Moon and Hee Jung Lee. Investigation: Sujin Moon. Methodology: Hee Jung Lee. Project administration: all authors. Resources: all authors. Software: Sujin Moon, Jung U Shin, Dong Hyun Kim, and Hee Jung Lee. Supervision: Hee Jung Lee. Validation: all authors. Visualization: Sujin Moon and Hee Jung Lee. Writing—original draft: Sujin Moon. Writing—review & editing: Yun Kyung Jang and Hee Jung Lee. Approval of final manuscript: all authors.

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