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Apocrine Gland—Rich Skin Has a Non-Inflammatory IL-17—Related Immune Milieu, that Turns to Inflammatory IL-17—Mediated Disease in Hidradenitis Suppurativa



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TO THE EDITOR

The pathogenesis of hidradenitis suppurativa/acne inversa (HS) is still unclear, but is likely initiated by follicular occlusion of the pilosebaceous-apocrine units (Hoffman et al., 2017) in the apocrine gland-rich (AGR) skin (armpits, intramammary fold, genital groin, perianal areas, and buttocks). The outstanding role of keratinocytes in the initiation phase was also highlighted by recently described signaling pathways (Notch and mTOR signaling, IL-36 pathway) related to HS pathophysiology (Balato et al., 2019; Di Caprio et al., 2017; Scala et al., 2018). Following keratinocyte activation, proliferation and follicular occlusion, immune cell infiltration, pro-inflammatory cytokine, and chemokine and antimicrobial peptide (AMP) production resulting in severe destruction of the surrounding tissue lead to fully developed immune-mediated inflammation.

In HS, IL-17 levels have been shown to be elevated (Schlapbach et al., 2011; Wolk et al., 2011) and IL-17 was proven to be produced mainly by inflammatory T helper 17 type lymphocytes (Kelly et al., 2015; Schlapbach et al., 2011). IL-17 is a multifaceted cytokine that has both physiological

and pathological, or in another classification non-inflammatory and inflammatory, roles at least on three different levels: i) During homeostatic conditions, it has a role in maintaining immune surveillance of barriers that cooperate with commensals; ii) it can also protect barrier surfaces during the invasion of extracellular pathogens; whereas iii) it appears to be one of the most prominent factors in the initiation and maintenance of autoimmunity and chronic inflammation (Abusleme and Moutsopoulos, 2017).

In our previous studies (Beke et al., 2018; Dajnoki et al., 2017), we reported that sebaceous gland-rich skin areas, considered as oily skin, similarly to the previously published topographical distinctions of the microbiota and the chemical milieu (Bouslimani et al., 2015; Grice and Segre, 2011), are equipped with a significantly different immune and barrier supply compared to sebaceous gland-poor areas, considered as dry skin. In the present project, we aimed to further analyze whether AGR areas (as analogous to moist skin in previous literature) also develop their characteristic immune and barrier milieu because these skin regions were proven to possess specific microbiota composition, chemical milieu, moisture

content, and temperature appreciably different from apocrine gland-poor (AGP) skin (AGP skin biopsies were taken also from dry skin, similarly to previous sebaceous gland-poor biopsies, containing neither apocrine nor sebaceous glands, detailed identification in [Supplementary Table S1](#) online) (Grice and Segre, 2011). We were interested in whether AGR skin's immune characteristics could predispose this region to develop specifically an IL-17-mediated inflammation, and also aimed to search for the downstream tissue effects of IL-17 in HS, because a systematic survey was missing.

Biopsies from axillary region (representing moist AGR skin, $n = 8$) and from shin and arm areas (representing dry AGP skin, $n = 8$) of healthy individuals and lesional axillary skin of HS patients ($n = 8$) were gained ([Supplementary Table S1](#)), after obtaining written informed consent, according to the Declaration of Helsinki principles, and analyzed by quantitative real-time PCR and immunohistochemistry (IHC), which was quantified by Panoramic Viewer software (3DHISTECH, Budapest, Hungary) after whole slide imaging. First, dendritic cell (DC) and T-cell characteristics of AGR were compared to AGP, then HS to AGR. The study was approved by the local ethics committee of University of Debrecen, Hungary.

IHC revealed significantly elevated numbers of CD11c⁺ DCs and CD4⁺ T cells in AGR region compared to AGP, without prominent DC activation. Although quantitative real-time PCR analyses showed no significant differences between the two regions in the

Abbreviations: AGP, apocrine gland-poor; AGR, apocrine gland-rich; AMP, antimicrobial peptide; CCL, chemokine (C-C motif) ligand; DC, dendritic cell; HS, hidradenitis suppurativa; IHC, immunohistochemistry

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Table 1. Comparison of immune and barrier components' expression in apocrine gland-poor, apocrine gland-rich, and hidradenitis suppurativa skin¹

Variable	AGR vs AGP					HS vs AGR				
	qRT-PCR		IHC		References ³	qRT-PCR		IHC		References ³
	P-Value	AGR vs AGP	P-Value	AGR vs AGP		P-Value	HS vs AGR	P-Value	HS vs AGR	
		(FC)		(FC) ²			(FC) ²		(FC) ²	
Components of adaptive immune response										
Cellular components										
CD4 ⁺ T cells	nd	nd	<0.0001	4.02 ↑	#	nd	nd	<0.0001	3.02 ↑	1–3
CD11c ⁺ DCs	nd	nd	0.001	2.99 ↑	#	nd	nd	0.038	1.74 ↑	3,4
CD80 ⁺ cells	0.825	0.83	nd	nd	#	0.018	18.39 ↑	nd	nd	#
CD83 ⁺ cells	0.714	1.26	0.020	2.25 ↑	#	0.008	2.26 ↑	0.003	2.90 ↑	#
CD86 ⁺ cells	0.683	0.70	nd	nd	#	0.004	2.94 ↑	nd	nd	#
CD1a ⁺ DCs	nd	nd	0.286	1.06	#	nd	nd	0.302	1.10	#
CD163 ⁺ cells	nd	nd	0.111	2.12	#	nd	nd	0.004	6.02 ↑	4
Th17-related factors										
IL-17A	0.191	0.61	0.0003	UDL in AGR	#	<0.0001	167.45 ↑	0.001	4.98 ↑	1–3,5
IL-10	0.322	0.72	0.0003	2.31 ↑	#	0.111	2.26	<0.0001	4.8 ↑	2,3,6,7
IL-1B	0.786	2.33	nd	nd	#	0.032	40.24↑	nd	nd	2,7
IL-6	0.333	1.01	nd	nd	#	0.206	1.66	nd	nd	3,6
IL-23A	0.481	1.22	nd	nd	#	0.001	3.43 ↑	nd	nd	1
TGFB1	0.206	0.71	nd	nd	#	0.016	2.61 ↑	nd	nd	6
RORC	0.095	0.82	nd	nd	#	0.056	0.43	nd	nd	#
Th1-related factors										
IL-12B	0.500	UDL in AGR	nd	nd	#	0.036	8.26 ↑	nd	nd	2,3
TBX21	0.536	0.74	nd	nd	#	0.016	6.18 ↑	nd	nd	#
IFNG	0.600	0.85	0.005	UDL in AGR	#	0.267	7.63	0.005	11.01 ↑	2,3,5,7
TNFA ⁴	0.222	0.62	0.083	UDL in AGR	#	0.016	1.90 ↑	0.001	22.61 ↑	4,7–9
Th2-related factors										
IL-13	UDL	UDL	0.142	2.12	#	UDL	UDL	0.143	1.47	3,10
GATA3	0.222	0.65	nd	nd	#	0.008	0.24	nd	nd	#
Th22-related factors										
IL-22	UDL	UDL	nd	nd	#	0.050	UDL in AGR	nd	nd	2,5
AHR	0.155	1.59	0.494	0.74	#	0.004	3.97 ↑	0.13	0.51	#
Treg-related factors										
FOXP3	>0.999	1.12	nd	nd	#	0.229	1.57	nd	nd	11
CCR4	>0.999	1.10	nd	nd	#	0.032	4.32	nd	nd	#
CCR8	0.714	0.70	nd	nd	#	0.802	0.90	nd	nd	#
Components of innate immune response and barrier molecules										
Chemokines										
CCL2 ⁴	0.714	1.37	0.004	5.08 ↑	#	0.222	1.59	0.012	4.64 ↑	#
CCL20 ⁴	0.857	0.73	0.004	2.4 ↑	#	0.016	3.89 ↑	0.004	6.79 ↑	5
CCL3	0.714	0.66	nd	nd	#	0.016	15.94 ↑	nd	nd	#
CCL19	0.857	0.82	nd	nd	#	0.029	4.05 ↑	nd	nd	#
CCL23	0.413	1.23	nd	nd	#	0.016	2.36 ↑	nd	nd	#
CCL24	0.250	2.69	nd	nd	#	0.571	1.59	nd	nd	#
Antimicrobial peptides										
TSLP	0.397	0.84	0.006	331.56 ↑	#	0.437	0.91	0.179	1.24	#
S100A7 ⁴	0.413	1.06	nd	nd	#	0.016	27.62 ↑	nd	nd	2,9,12
S100A8 ⁴	0.667	1.21	0.171	2.34	#	0.016	30.75 ↑	0.029	5.82 ↑	2,12,13
S100A9 ⁴	0.413	1.70	nd	nd	#	0.016	28.38 ↑	nd	nd	2,12,13
DEFB4B ⁴	0.571	2.02	nd	nd	#	0.016	113.67 ↑	nd	nd	6,8,12
LCN2 ⁴	0.310	3.87	0.004	1.38 ↑	#	0.008	7.13 ↑	0.018	6.4 ↑	14

(continued)

expression of T-cell–related factors, by IHC both IL-17⁺ and IL-10⁺ cells were detected in significantly elevated

numbers in AGR and were nearly absent from AGP. Moreover, a few IFN-γ⁺ cells were found in AGR only, and were

totally absent from AGP (Table 1, Supplementary Figures S1 and S2 online).

Table 1. Continued

Variable	AGR vs AGP					HS vs AGR				
	qRT-PCR		IHC		References ³	qRT-PCR		IHC		References ³
	AGR vs AGP		AGR vs AGP			HS vs AGR		HS vs AGR		
	P-Value	(FC)	P-Value	(FC) ²		P-Value	(FC) ²	P-Value	(FC) ²	
Barrier molecules										
LOR ⁴	0.825	1.02	0.158	0.74	#	0.310	0.69	0.036	0.7 ↓	#
FLG ⁴	0.110	1.68	0.037	0.8 ↓	#	0.395	2.99	0.095	1.60	#
CLDN1	0.679	1.31	nd	nd	#	0.310	0.67	nd	nd	#
KRT17 ⁴	0.262	1.10	0.329	1.14	#	0.009	2.94 ↑	0.008	5.62 ↑	15,16
KRT79	0.036	14.55 ↑	nd	nd	#	0.222	0.44	nd	nd	#
Proinflammatory molecules										
TLR2	0.825	1.25	nd	nd	#	0.048	5.16 ↑	nd	nd	4,6
TLR4	>0.999	0.88	nd	nd	#	0.018	3.38 ↑	nd	nd	6
NLRP3	0.191	0.91	nd	nd	#	0.071	4.21	nd	nd	13
IL-1B ⁴	0.786	2.33	nd	nd	#	0.032	40.23 ↑	nd	nd	2,7
TNFA ⁴	0.222	0.62	0.083	UDL in AGP	#	0.016	1.89 ↑	0.001	22.61 ↑	4,7–9

Abbreviations: AGP, apocrine gland–poor; AGR, apocrine gland–rich; CCL, chemokine (C-C motif) ligand; DC, dendritic cell; FC, fold change; HS, hidradenitis suppurativa; IHC, immunohistochemistry; nd, not determined; qRT-PCR, quantitative real-time PCR; Th, T helper; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TNFA, tumor necrosis factor-α; Treg, regulatory T; UDL, under detection limit.

¹Statistical analyses between protein and mRNA levels were determined by one-way analysis of variance followed by Newman–Keuls post-hoc test. Bold type indicates data with significant differences.

²Arrows indicate the direction of significant changes.

³# represents data that are previously unreported, to our knowledge. Eight samples were examined in each group regarding all the investigated molecules. Numbers (1–16) represent publications of other groups in connection with the given molecules in HS. The list of these publications can be found in the [Supplementary References](#) online.

⁴IL-17–related (downstream) factor.

In HS, the numbers of DCs and T cells further and significantly increased, DCs became activated, and CD163⁺ macrophages appeared in a significantly enhanced number compared to AGR (IHC). Significantly higher expression of T-helper 17–related (IL-1B, IL-17A, IL-23A, transforming growth factor-β1) and even T-helper 1–related molecules (IL-12B, TBX21, tumor necrosis factor-α) were detected at the mRNA level. Furthermore, by IHC, the number of IL-17⁺ and IL-10⁺ cells further and significantly increased, and a robust presence of tumor necrosis factor-α⁺ and IFN-γ⁺ cells became detectable (Table 1, [Supplementary Figures S1, S2, and S3](#) online).

In the second part of our experiments, we investigated important chemokines, AMPs, barrier and pro-inflammatory molecules of the skin immune system. Although, when comparing AGR to AGP skin, no significant difference could be detected at the mRNA level, except for the higher expression of KRT79 in AGR, protein levels of IL-17–related chemokines (CCL2, CCL20), AMPs (TSLP, LCN2), and one of the barrier molecules (FLG)

were significantly altered in AGR (Table 1, [Supplementary Figure S3](#)).

When comparing HS and AGR samples, quantitative real-time PCR revealed significantly increased expression of chemokines (CCL3, CCL19, CCL20, CCL23) and AMPs (DEFB4B, S100A7, S100A8, S100A9, LCN2), as well as altered mRNA level of KRT17 barrier molecule in HS. The significantly and highly elevated level of T-helper 17–related chemokines (CCL2, CCL20) and AMPs (S100A8, LCN2) were also confirmed by IHC, together with the altered expression of barrier molecules (KRT17, LOR), which also reflected an IL-17 effect (Table 1, [Supplementary Figure S3](#)).

Expression of pro-inflammatory molecules (Toll-like receptor 2, Toll-like receptor 4, NLRP3, IL-1β, tumor necrosis factor-α) was low in both AGP and AGR, while in HS, a robust and significant increase was observed in their mRNA and protein levels, with the exception of NLRP3 (Table 1, [Supplementary Figure S3](#)).

In our present study, we could unambiguously show that moist/AGR skin possesses distinct immune and barrier milieu compared to dry/AGP

areas. This is a non-inflammatory IL-17/IL-10–containing environment with significantly higher T cell and DC attendance, without any signs of activation or inflammation, accompanied by IL-17–related chemokines, AMPs, and barrier characteristics. TSLP presence can be considered as part of the homeostatic immune milieu of AGR, similar to sebaceous gland–rich skin or the colonic mucosa ([Dajnoki et al., 2017](#); [Ziegler and Artis, 2010](#)).

Previous data have shown a subclinical inflammatory state preceding the manifestation of HS, which is started with an aberrant keratinocyte response to commensal follicular bacteria ([Kelly et al., 2014](#); [Prens and Deckers, 2015](#)). Healthy AGR skin disposes region-specific microbiota influenced by the chemical milieu, moisture content, and temperature of this area, but in accordance with our present results, this specific commensal population can live in a homeostatic state with the region-specific immune and barrier milieu of AGR skin. We hypothesize that, during the development of HS, this “AGR-specific” homeostatic symbiosis between microbiota and skin immune system can be modified (or not fully

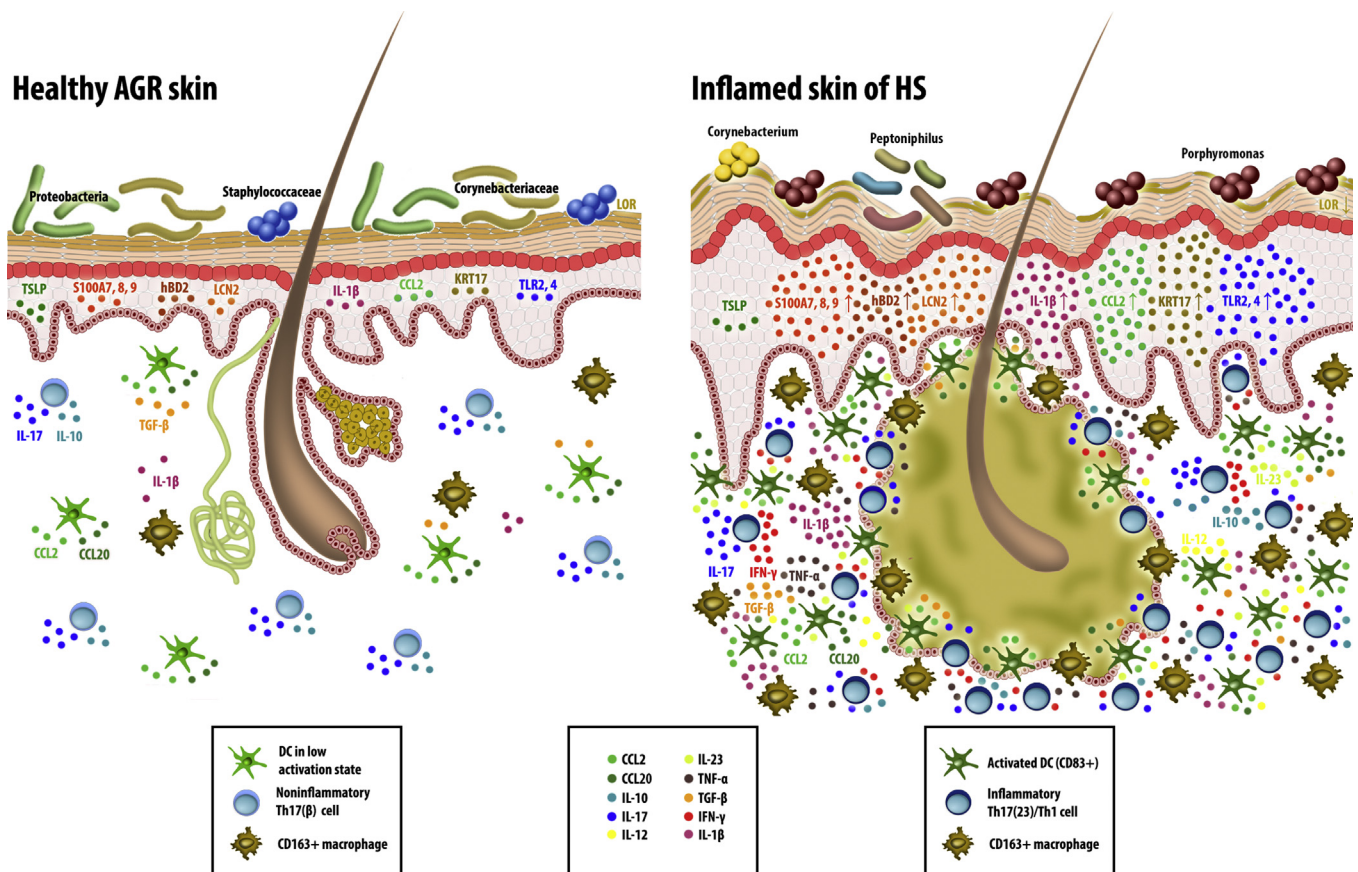


Figure 1. Apocrine gland-rich skin has a non-inflammatory IL-17-related immune milieu, which turns to inflammatory IL-17-mediated disease in hidradenitis suppurativa. Healthy apocrine gland-rich skin disposes region-specific microbiota, but this specific commensal population can live in a homeostatic state with the region-specific immune and barrier milieu of apocrine gland-rich skin. During development of hidradenitis suppurativa, this “apocrine gland-rich-specific” homeostatic symbiosis between microbiota and skin immune system can be modified (or not even fully developed), and this breakdown of the non-inflammatory IL-17/IL-10 milieu leads to a severe IL-17/IFN-γ-type inflammation in hidradenitis suppurativa. Microbiota of healthy apocrine gland-rich and lesional hidradenitis suppurativa skin was presented according to the findings of Grice and Segre (2011) and Ring et al. (2017), respectively. AGR, apocrine gland-rich; CCL, Chemokine (C-C motif) ligand; DC, dendritic cell; HS, hidradenitis suppurativa; Th17(β), non-inflammatory T-helper 17; Th17(23), inflammatory T-helper 17; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α.

developed), and this alteration of the non-inflammatory IL-17/IL-10 milieu leads through a gradual subclinical progression to a severe IL-17/IFN-γ-type apparent inflammation in HS (Figure 1). The mentioned pathomechanism of HS highly resembles that of Crohn’s disease, as proposed by current literature (Maloy and Powrie, 2011; van der Zee et al., 2016), which can be an additional link between the two diseases.

The data of our study also suggest that the non-inflammatory IL-17 milieu of AGR skin may prone this area to develop specifically an IL-17 type inflammatory disease, as all the characteristic adaptive and innate immune or barrier features of AGR skin were also present in HS in robust and widespread forms, accompanied by activation and inflammation markers, ultimately

resulting in a full-blown inflammatory IL-17 environment (Table 1, Supplementary Figures S1–S3). This inflammatory IL-17 milieu was reflected by significant chemokine, AMP, and barrier alterations (Table 1). High IFN-γ and tumor necrosis factor-α presence in HS was also confirmed by this study, although previous literature data were inconsistent regarding their levels (Kelly et al., 2014).

In conclusion, our previous and present data suggest that not only the microbiota and chemical content of human skin show three main topographical areas (dry, moist, oily/sebaceous), but probably in correlation to this, the immune and barrier characteristics of these topographical regions are also distinct, which can make these skin regions become prone to the development of “region-

specific” inflammatory skin diseases, like HS on AGR and acne (Mattii et al., 2018) and rosacea (Dajnoki et al., 2017) on sebaceous gland-rich areas.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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A. Jenei^{1,2,9}, Z. Dajnoki^{1,2,9},
B. Medgyesi^{1,2}, K. Gáspár^{1,2},
G. Béke^{1,2}, Á. Kinyó³, G. Méhes⁴,

Z. Hendrik⁴, T. Dinya⁵, D. Töröcsik²,
C.C. Zouboulis⁶, E.P. Prens⁷, T. Bíró⁸,
A. Szegedi^{1,2,10} and A. Kapitány^{1,2,10,*}

¹Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; ²Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; ³Department of Dermatology, Venereology, and Oncodermatology, University of Pécs, Pécs, Hungary; ⁴Department of Pathology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; ⁵Department of Surgery, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; ⁶Departments of Dermatology, Venereology, Allergology, and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany; ⁷Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands; and ⁸Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

⁹These authors equally contributed to this work.

¹⁰These authors equally contributed to this work.

*Corresponding author e-mail: anikokapitany@gmail.com

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <https://doi.org/10.1016/j.jid.2018.10.020>

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The Comparison of Skin Transcriptomes Confirms Canine Atopic Dermatitis Is a Natural Homologue to the Human Disease

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TO THE EDITOR

Atopic dermatitis (AD) is a common chronic recurrent allergic skin disease with an estimated prevalence of 10% in adult humans and up to 20% in children; the salient immune-mediated clinical features of this disease have

been reviewed recently (Weidinger and Novak, 2016). In the last decade, much progress has been made to better characterize the pathogenesis of human AD. The pathomechanism of human AD involves the complex interplay of primary and secondary epidermal

barrier defects with associated T-helper (Th) 2 and Th22 immune responses in most individuals, with a more complex reaction in children and some Asian subpopulations, who also exhibit a Th17 polarization (Brunner et al., 2017; Weidinger and Novak, 2016).

Animal models play a critical role for studying the mechanism of lesion formation and developing novel therapies for AD. Although various domestic animals are affected by eczema (Einhorn et al., 2018; Gershwin, 2015), dogs

Abbreviations: AD, atopic dermatitis; Th, T helper

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