A new T helper 17 cytokine in hidradenitis suppurativa: antimicrobial and proinflammatory role of interleukin-26

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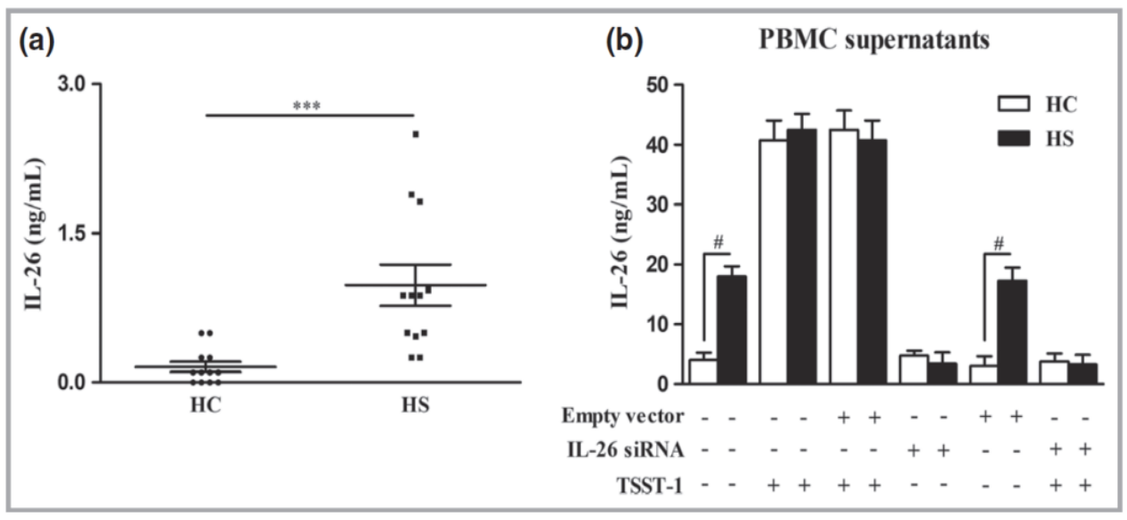
Introduction IL-26 is a Th-17 cytokine that has been described like a pro-inflammatory and antimicrobial mediator. So far, IL-26 has been reported in several immune-mediated inflammatory diseases, but its involvement in inflammatory skin disorders is poorly known.

Methods IL-26 was assessed in HS patients through gene expression and protein analysis at skin and circulating levels. *Ex vivo* HS organ skin cultures, together with IL-26 antibody treatment, were performed to determine the IL-26 activity. PBMCs from patients with HS and healthy controls (HC) were either silenced or not with IL-26 siRNA in order to measure its antimicrobial, cytotoxic and phagocytic activities against *Staphylococcus aureus*.

Clinical and demographic characteristics of HS patients (n = 12)

Male, n (%)	3 (25)
Age (years)	27·3 ± 8·32
Disease duration (years)	7·42 ± 4·19
Family history (yes), n (%)	2 (17)
Body mass index (kg m^{-2})	28·4 ± 3·6
iHS4	6·25 ± 2·49
Sartorius score	61·1 ± 10·1

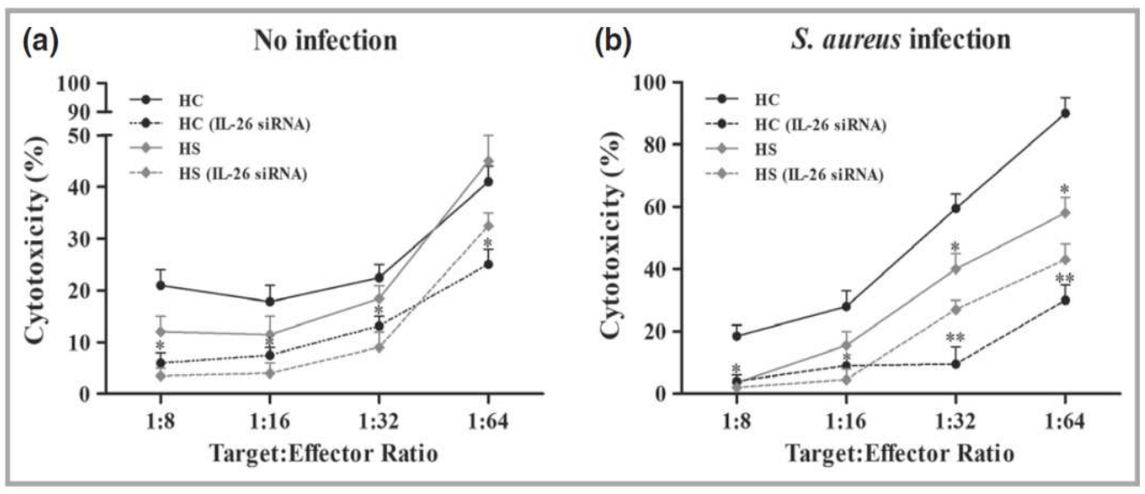
Data are given as the mean ± SD unless stated otherwise. iHS4, International Hidradenitis Suppurativa Severity Score System.



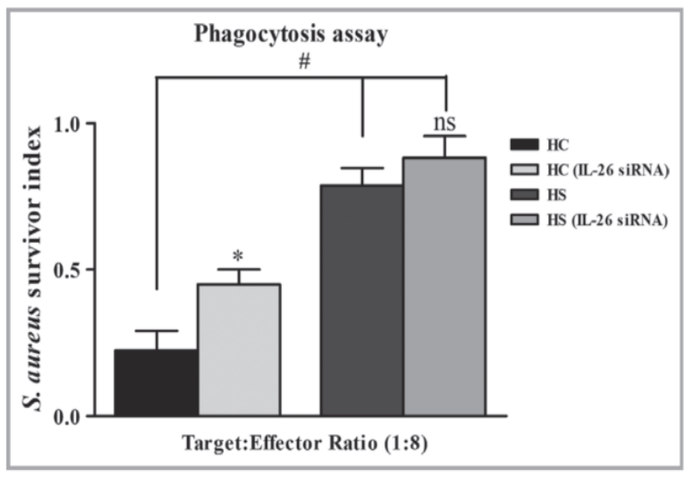
Result 1 (a) IL-26 plasma levels were increased in HS patients compared to HC. (b) Cultured HS PBMCs (n=5) produced higher basal levels of IL-26 than HC PBMCs (n=5). TSST-1 stimulation (100 ng mL^{-1}) induced a comparable increase of IL-26 in both HS and HC PBMCs. IL-26 silencing was able to shut down IL-26 production in HS PBMCs (TSST-1 stimulated or not) and in TSST-1-stimulated HC PBMCs. ***P<0001 and #P<005 were calculated using the Mann–Whitney test.

	IC_{50} value	
Samples	*P. aeruginosa*	*S. aureus*
HC resting	NI	NI
HC + TSST-1	NI	125 µg/mL
HC IL-26 siRNA	NI	NI
HC IL-26 siRNA + TSST-1	NI	NI
HS resting	NI	NI
HS + TSST-1	NI	NI
HS IL-26 siRNA	NI	NI
HS IL-26 siRNA + TSST-1	NI	NI

Result 2 *P. aeruginosa* or *S. aureus* were incubated with increasing concentrations of supernatants (from 125 to 1000 µg mL^{-1}) from HS PBMCs in resting, TSST-1-stimulated and IL-26-silenced conditions. Supernatants from resting and silenced HS PBMCs were totally inactive for both bacterial strains. Likewise, HS PBMC supernatants previously stimulated with TSST-1 did not inhibit *S. aureus* growth as observed HC. Bacterial growth was measured as the optical density at 600 nm per mL. NI, no inhibition.

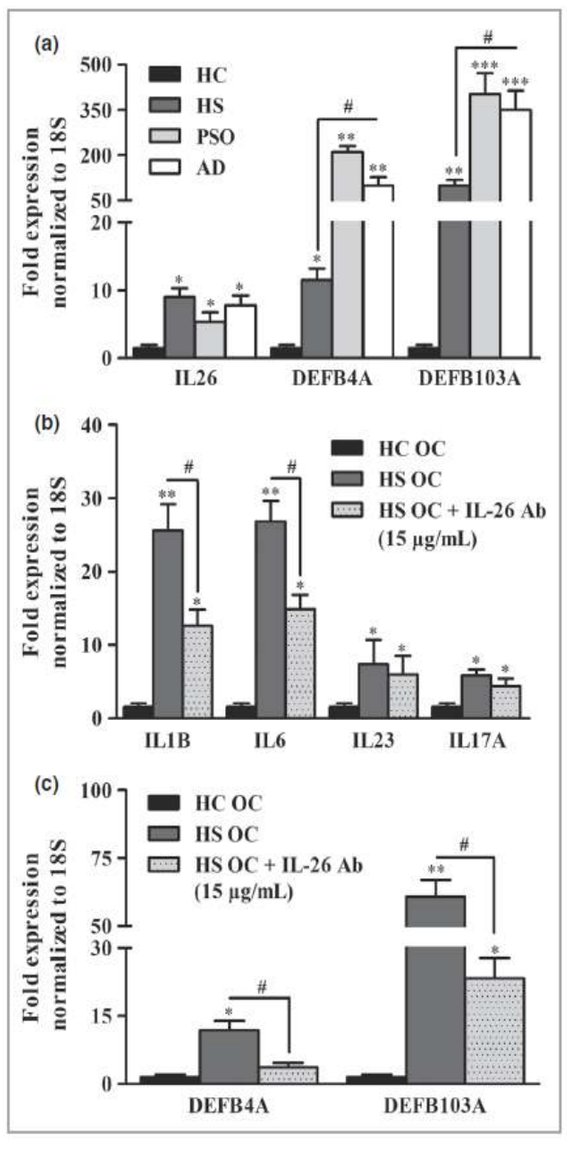


Result 3 (a) Cytotoxic activity of HC PBMCs (n=5) against HaCaT cells (1:2500) was comparable to HS PBMCs (n=5). (b) HS PBMC cytotoxicity against HaCaT cells infected by *S. aureus* was significantly decreased compared with HC PBMCs at almost all analysed ratios. IL-26 transfection was able to reduce significantly the capacity of HC PBMCs to kill the target cells. Conversely, silenced HS PBMCs showed no significant difference compared with HS unsilenced cells. *P<005, **P<001 were calculated using the Wilcoxon matched-pairs test (transfected vs. nontransfected) or Mann–Whitney test (HS vs. HC nontransfected).



Result 4 Survival index of *Staphylococcus aureus* in the presence of PBMCs transfected or not with IL26 siRNA from HC (n = 5) and HS patients (n = 5). At a target–effector ratio of 1 : 8, HS PBMCs showed a lower phagocytic activity than PBMCs from healthy donors.

Interestingly, silencing experiments were able to reduce significantly the phagocytosis of control PBMCs, whereas no significant differences were observed between silenced and unsilenced HS PBMCs. *P < 005 (transfected vs. nontransfected) calculated using Wilcoxon matched-pairs test, #P < 005 (HS vs. HC nontransfected) calculated using Mann–Whitney test.



Result 5 (a) IL26 expression was significantly enhanced in HS, psoriasis (PSO) and atopic dermatitis (AD) lesional skin compared to HC skin. A significant decrease was found for both DEFB4A and DEFB103A (encoding HBD2 and HBD3, respectively) in HS vs. PSO and AD skin, whereas this was not detected for IL26. (b) HS lesional skin was used to perform an *ex vivo* organ culture in the presence and absence of IL-26 neutralizing Ab (15 lg mL^{-1}). Gene expression of IL1B and IL6 was significantly decreased by IL-26 Ab treatment, whereas IL23A and IL17A were not affected. (c) IL-26 inhibition was able to reduce significantly the expression of DEFB4A and DEFB103A. *P<005, **P<01, ***P <0.001 vs. HC; #P<005 between PSO, AD and HS, calculated using the Mann–Whitney test. #P<005 for IL-26 Ab treatment vs. nontreatment, calculated using the Wilcoxon matched-pairs test.

Conclusions We have expanded the significance of IL-26 as an inducer of proinflammatory and antimicrobial mediators. Our findings suggest that infection susceptibility in HS might be related to IL-26. Although the role of bacteria remains controversial in HS, this study supports that there is a defect of antimicrobial response in these patients.