Published in final edited form as:

Br J Dermatol. 2010 September ; 163(3): 659–661. doi:10.1111/j.1365-2133.2010.09892.x.

History of eczema herpeticum is associated with the inability to induce human β -defensin (HBD)-2, HBD-3 and cathelicidin in the skin of patients with atopic dermatitis

T.R. Hata, P. Kotol, M. Boguniewicz*, P. Taylor*, A. Paik, M. Jackson, M. Nguyen, F. Kabigting, J. Miller, M. Gerber, D. Zaccaro†, B. Armstrong†, R. Dorschner, D.Y.M. Leung*, and R.L. Gallo

Division of Dermatology, Department of Medicine, University of California San Diego, 9350 Campus Point Drive, La Jolla, CA 92037, U.S.A. and VA Healthcare System, San Diego, U.S.A

*Division of Pediatric Allergy-Immunology, National Jewish Health, Denver, CO, U.S.A.

†Rho Inc., Chapel Hill, NC, U.S.A.

Keywords

ADEH; AMPs

MADAM, Patients with atopic dermatitis (AD) with a history of eczema herpeticum (ADEH) represent a subset of individuals with AD who have more severe disease.¹ It has previously been shown that the skin of patients with AD has defects in its capacity to increase maximally the antimicrobial peptides (AMPs), cathelicidin, human β -defensin (HBD)-2 and HBD-3 in response to inflammation, in contrast to patients with psoriasis who also have inflammation of the skin, but no difficulty with AMP induction.^{2,3} To date, however, previous studies have not examined HBD-2 and HBD-3 induction in the ADEH subset of patients.⁴ We sought to examine if subjects with ADEH exhibit an inhibition in induction of AMPs, compared with subjects without ADEH. A total of 81 subjects were recruited into the study: 26 patients with psoriasis, 21 with AD and nine with ADEH and 25 healthy subjects with no history of skin disease (Table S1, see Supporting information). Two 2-mm punch biopsies were collected from lesional and nonlesional skin of the patients. Normal controls provided two 2-mm punch biopsies from the skin of their upper inner arm. Quantification of cathelicidin, interleukin (IL)-13, HBD-2 and HBD-3 in the skin was performed by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) (see supporting information), and their expression was calculated as relative to glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) mRNA. All statistical analyses were performed using SAS v9.1 or higher (SAS Institute, Cary, NC, U.S.A.) (see Supporting information).

Compared with individuals with AD or psoriasis, patients with ADEH showed a lesser relative increase in cathelicidin, HBD-2 and HBD-3 mRNA in their lesional skin (Fig. 1). Immunohistochemical staining of LL-37 confirmed the RT-PCR data for this peptide product of the cathelicidin gene (Fig. S1, see Supporting information) and supported a prior report that cathelicidin is suppressed in subjects with ADEH.⁴ This finding, combined with the novel observation of decreased inducibility of HBD-2 and HBD-3, suggests that HBD-2

Correspondence: Tissa Hata and Richard Gallo. thata@ucsd.edu; rgallo@vapop.ucsd.edu.

Conflicts of interest: none declared.

Supporting information Additional supporting information may be found in the online version of this letter.

and HBD-3 may further contribute to the increased incidence of secondary infection with herpes simplex virus (HSV) in ADEH.

As expected, due to low expression in normal skin, nonlesional skin revealed no differences in cathelicidin levels between the four groups (Fig. 2).⁵ Interestingly, however, nonlesional HBD-2 levels were significantly higher in patients with ADEH compared with those with AD ($P < 0.001$) or psoriasis ($P < 0.001$) and normal controls ($P = 0.001$). Nonlesional HBD-3 levels were also higher in patients with ADEH compared with those with AD ($P = 0.002$) or psoriasis ($P = 0.003$). Upregulation of HBD-2 and HBD-3 has been shown to occur with proinflammatory stimuli such as tumour necrosis factor (TNF)- α and interferon (IFN)- γ through signal transducer and activator of transcription (STAT)-1 and nuclear factor- κ B, and inhibition through IL-4 and IL-13 to activate STAT-6 to induce the suppressors of cytokine signalling (SOCS)-1 and SOCS-3 which inhibit TNF- α and IFN- γ .⁶ The presence of nonpathogenic organisms such as *Staphylococcus epidermidis* may be the signal for the induction of TNF- α or IFN- γ , which may outweigh the downregulatory effects of IL-13 and IL-4.

Significantly higher serum IgE levels were observed in subjects with ADEH than in patients with AD ($P < 0.001$) or controls ($P < 0.001$), suggesting that the T-helper (Th) 2 phenotype is more prominent in individuals with ADEH compared with patients with AD. Examination of lesional minus nonlesional skin cathelicidin levels for patients with ADEH and AD combined revealed a significant negative correlation with total serum IgE ($r = -0.602$, $P = 0.018$), again indicating that increased Th2 polarity reduces the ability of the atopic skin to induce cathelicidin during inflammation (Fig. S2, see Supporting information).

Finally, as IL-13 has been associated with the Th2 phenotype, IL-13 levels were analysed to determine if the cytokine milieu differed in lesional and nonlesional skin. Lesional IL-13 levels were significantly higher in subjects with ADEH than in patients with AD ($P = 0.018$) or psoriasis ($P < 0.001$). Nonlesional IL-13 levels also presented a similar trend, with levels in ADEH nonlesional skin significantly higher than in the nonlesional skin of patients with AD ($P = 0.005$) or psoriasis ($P = 0.014$). As expected, lesional IL-13 levels of subjects with ADEH and AD combined showed a positive correlation with total IgE ($r = 0.699$, $P = 0.017$) (Fig. S3, see Supporting information).

In summary, our study shows that there is a defect in the inducibility of the AMPs, HBD-2, HBD-3 and cathelicidin, in patients with ADEH. This indicates that individuals with ADEH are deficient in several AMPs, which may account for their increased risk of infections with *Staphylococcus aureus* and HSV as well as their propensity for eczema vaccinatum. Nonlesional skin values for HBD-2 and HBD-3 are not depressed in patients with ADEH compared with those with AD, normal controls or patients with psoriasis. These observations suggest that analysis of AMP expression may be a useful tool for the prediction of superinfection in individuals with AD; however future studies with larger numbers of patients may be necessary to confirm this finding. Furthermore, understanding the factors that contribute to the suppression of AMP expression in AD can help inform the design of novel strategies for correcting this defect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH/NIAID contracts N01 AI 40029, N01 AI40033.

References

1. Beck LA, Boguniewicz M, Hata T, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol.* 2009; 124:260–9. 269.e1–7. [PubMed: 19541356]
2. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med.* 2002; 347:1151–60. [PubMed: 12374875]
3. Nomura I, Goleva E, Howell MD, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol.* 2003; 171:3262–9. [PubMed: 12960356]
4. Howell MD, Wollenberg A, Gallo RL, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol.* 2006; 117:836–41. [PubMed: 16630942]
5. Schaubert J, Dorschner RA, Coda AB, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest.* 2007; 117:803–11. [PubMed: 17290304]
6. Albanesi C, Fairchild HR, Madonna S, et al. IL-4 and IL-13 negatively regulate TNF-alpha and IFN-gamma-induced beta-defensin expression through STAT-6, suppressor of cytokine signaling (SOCS)-1, and SOCS-3. *J Immunol.* 2007; 179:984–92. [PubMed: 17617590]

Fig 1.

(a) Ability to induce antimicrobial peptides (AMPs) as evidenced by lesional minus nonlesional expression analysed by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR). Skin biopsy samples from lesional and nonlesional skin of subjects were collected and analysed for expression of AMPs. Values of the AMPs were normalized to the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) and the data plotted are presented as relative AMP expression. Differences separated by diagnostic group reveal cathelicidin expression in patients with atopic dermatitis (AD) with a history of eczema herpeticum (ADEH) to be significantly depressed compared with patients with AD ($P = 0.014$) or psoriasis ($P = 0.001$). (b) Ability to induce human β -defensin (HBD)-2 as evidenced by lesional minus nonlesional expression, analysed by quantitative RT-PCR and normalized to the housekeeping gene *GAPDH* reveal HBD-2 to be significantly suppressed in patients with ADEH in comparison to those with AD ($P = 0.003$) or psoriasis ($P < 0.001$). (c) Ability to induce HBD-3 as evidenced by lesional and nonlesional differences, analysed by quantitative RT-PCR and normalized to the housekeeping gene *GAPDH* reveal HBD-3 expression in patients with ADEH to be depressed compared with that in patients with psoriasis ($P = 0.003$), while showing a trend towards lower levels than subjects with AD ($P = 0.06$). (a–c) Differences were calculated using the $\Delta\Delta C_t$ method (see Supporting information).

Fig 2.

(a) Nonlesional skin values for cathelicidin analysed by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) and normalized to the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) revealed no significant differences between the four groups. (b) Analysis of human β -defensin (HBD)-2 in nonlesional skin revealed significantly higher HBD-2 levels in subjects with atopic dermatitis (AD) with a history of eczema herpeticum (ADEH) compared with patients with AD ($P < 0.001$) or psoriasis ($P < 0.001$), or normal control subjects ($P = 0.001$). (c) Analysis of HBD-3 in nonlesional skin revealed significantly higher HBD-3 levels in subjects with ADEH compared with those with AD ($P = 0.002$) or psoriasis ($P = 0.003$). CATH, cathelicidin; NonLes, nonlesional; Psor, psoriasis; Cont, control.