



Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.intl.elsevierhealth.com/journals/jods



Letter to the Editor

Possible role of nerve growth factor and interleukin-18 in pathogenesis of eczematous lesions of atopic dermatitis^a

ARTICLE INFO

Keywords:

Interleukin-18
Atopic dermatitis
Neuropeptides
Nerve growth factor

Data suggest that Th2 and Th1 cytokines contribute to the pathogenesis of AD with relative contribution of each cytokine dependent on duration of the skin lesions. T-cell responses being significantly tilted towards Th2 lymphocyte activity in patients with eczematous (acute) lesions; that is secretion of IL-4, IL-5 and IL-13; leading to IgE mediated immune reactions, in contrast to Th1 lymphocyte responses, in which IL-2 and IFN- γ are the predominant cytokines [1].

Nerve growth factor (NGF) is able to exert a variety of effects on immune-inflammatory cells and may participate in the pathogenesis and development of AD lesions, while IL-18 has a diverse ability to cross regulate Th1/Th2 derivation and function [2], both these proteins may interact with IgE.

A total of 17 patients 11 males and 6 females whose ages ranged from 5 to 14 years fulfilling the Hanifin and Rajka guidelines for diagnosis of AD presenting to Kasr El Aini Hospital's Dermatology Out-Patient Clinic were selected for this study. Disease severity was determined using the six areas, six sign atopic dermatitis (SASSAD) severity score. Patients' serum IgE, NGF and interleukin-18 (IL-18) levels were determined and a 4–5 mm punch skin biopsy was obtained from eczematous lesional skin of each patient. The control group consisted of seven males and three female healthy subjects with ages ranging between 8 and 13 years. Punch biopsies (4–5 mm) from this group's apparently healthy skin was obtained.

Table 1a shows the descriptive analysis of patient group. Normal range of IgE is 135 ± 9.7 kU/L, of NGF is 30.4 ± 9.4 pg/ml and of IL-18 is 125.8 ± 37 pg/ml. The NGF mRNA was higher in atopic lesional skin than controls, where it ranged from 784 to 1180 μ g/mg tissue with a mean of 920.3 ± 122.6 in atopic lesions and a range from 508 to 686 μ g/mg tissue and a mean of 602.1 ± 73.7 in controls. Statistically, this difference was highly significant ($P < 0.0001$; Table 1b). Also, IL-18 was expressed in the tissue specimens from all AD patients and healthy controls, where it was higher in AD than in controls, in a statistically significant manner ($P < 0.001$; Table 1b). In situ hybridization technique was done to identify cells that express NGF gene. NGF mRNA signals were present in mast cells, keratinocytes, and fibroblasts (Fig. 1a). Also, keratinocytes express IL-18 and

the signals were detected by in situ hybridization technique (Fig. 1b). Positive correlations between NGF, IL-18 and serum IgE level were statistically significant ($P < 0.012$ and $P < 0.004$, respectively).

The significant increase in NGF mRNA levels we detected in AD patients may lead to (1) T and B lymphocytes proliferation, (2) differentiation and activation of eosinophils, (3) mast cell degranulation and hyperplasia and (4) enhance GM-CSF activity, in addition to (5) NGF's own independent chemoattractant ability, and (6) its stimulatory effect on the extension and function of peripheral sensory neurons that may directly or indirectly participate in the provocation of itch in AD [3]. Finally, the regulatory effect of NGF on other neuropeptides may also be involved in AD, as primary afferent fibers can retrogradely transport NGF produced by their target cells to the dorsal root ganglion cells in which NGF can regulate the synthesis of other neuropeptides such as substance P, calcitonin gene related peptide and vasoactive intestinal polypeptide which may be involved in the pathogenesis of AD [4].

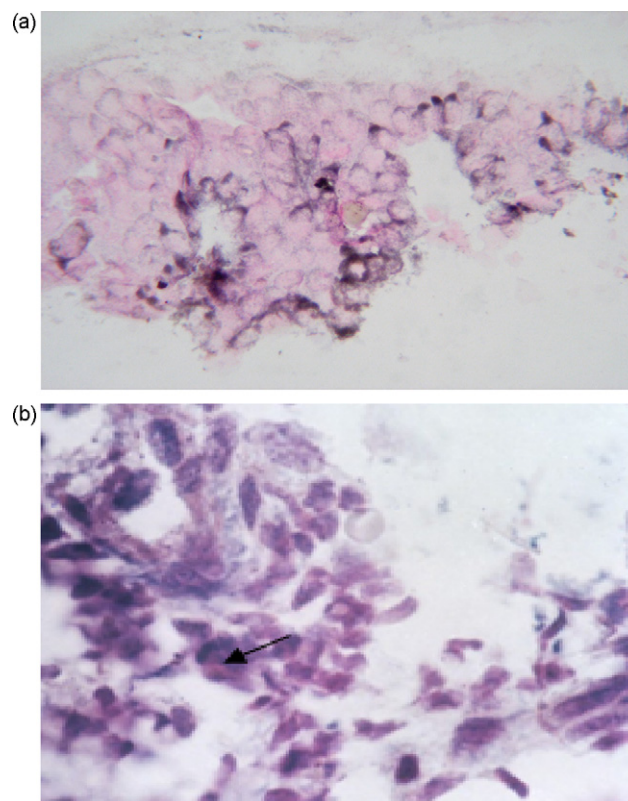


Fig. 1. (a) A photomicrograph of a skin section positive for mRNA-NGF. The positive signals could be seen mainly in the keratinocytes, fibroblasts and mast cells. (b) A photomicrograph of a skin section positive for mRNA-IL-18. The positive signals seen mainly in the keratinocytes.

Table 1a

Descriptive analysis of controls and patients groups

	Age	Disease duration (years)	SASSAD score	Serum IgE (kU/L)		Serum NGF (pg/ml)		Serum IL-18 (pg/ml)	
				Control	Patient	Control	Patient	Control	Patient
Mean $\pm$ S.D.	8.41 $\pm$ 2.8	6.15 $\pm$ 3.2	29.63 $\pm$ 9.4	135 $\pm$ 9.7	977.9 $\pm$ 1386.1	30.4 $\pm$ 9.4	519.9 $\pm$ 212.1	125.8 $\pm$ 37	401.2 $\pm$ 167.3
Median	8.0	6.0	28	125	481	28	512.6	112	389
Minimum	5	0.5	18	102	33	23	408.1	104	209
Maximum	14	10	53	158	4930	44	624.9	140	615

Table 1bComparison between quantities of NGF and IL-18 mRNAs in atopic and control group (μ g/mg tissue)

	NGF in atopic skin	NGF in control skin	IL-18 in atopic skin	IL-18 in control skin
Mean $\pm$ S.D.	920.29 $\pm$ 122.6	602.1 $\pm$ 73.7	1001.9 $\pm$ 286.6	612.9 $\pm$ 75.5
Median	898	600	974	626
Minimum	784	508	791	513
Maximum	1180	686	2043	692
P value	0.0001		0.001	

NGF in atopic lesional skin can be derived from different cells able to release this NP. Toyoda et al. [5] suggested that the increased plasma concentrations of NGF in patients with AD could partly result from the enhancement, activation and proliferation of eosinophils, Th2 cells and/or mast cells. Mast cells, eosinophils and Th2 cells are abundant in AD lesional skin where they liberate their cytokines and proteins (including NGF). Therefore, we propose that these cells may be responsible for the elevated levels of NGF not only in plasma of atopic patients, but also in AD lesional skin. It was also suggested that KC in severe AD might release greater amounts of NGF, which in turn may contribute to the subsequent increase in plasma levels of KC-derived NGF in parallel to the disease severity [2]. Further studies are needed for identification of cells involved in NGF production in AD lesional skin. The correlation between tissue levels of NGF mRNA and serum IgE, this may possibly be related to mast cells release of NGF in response to IgE [6].

The elevated serum and tissue IL-18 levels we detected in AD patients may enhance eosinophil recruitment, induces proliferation and recruitment of neutrophils by induction of GM-CSF. In combination with IL-2, it increases IL-13 production and in the presence of IL-3, it induces basophils and mast cells to express high levels of IL-13 and histamine [7,8]. The latter may stimulate the production of IL-18 in peripheral blood mononuclear cells. There may be a positive feed back regulation between histamine and IL-18. Moreover, some bacterial DNA motifs induce IL-18 secretion by activation of Toll like receptors (TLR-9) resulting in IL-18 dependent AD skin lesions [7].

Tissue IL-18 levels were positively correlated to serum IgE in a statistically significant manner. It was found that daily administration of IL-18 to transgenic mice caused a striking dose dependent increase in serum IgE in vivo [9]. Furthermore, transgenic mice over-expressing human caspase-1 in keratinocytes, in which there is high serum IL-18, develop dermatitis resembling AD skin lesions, with high serum IgE [9].

Unlike Yoshizawa et al. [10] we did not detect a correlation between IL-18 serum levels and clinical activity of AD.

We suggest that IL-18 acting as a pro Th2 mediator may be involved in the pathogenesis of acute AD lesions. We cannot however overlook the fact that, IL-18 can function as a pro Th1, and chronic AD skin lesions are Th1 $\geq$ Th2 cytokine mediated, therefore studying IL-18, together with IFN- γ in both acute and chronic AD skin lesions is recommended.

It seems that IL-18 and NGF are upregulated in AD and that both these proteins interact with IgE in different manners, possibly contributing to the pathogenesis of this disease.

References

- [1] Higashi N, Gesser B, Kawana S, Thestrup-Pedersen K. Expression of IL-18 mRNA and secretion of IL-18 are reduced in monocytes from atopic dermatitis. *J Allergy Clin Immunol* 2001;108:607–14.
- [2] Toyoda M, Nakanui M, Makino TI. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. *Br J Dermatol* 2002;147:71–9.
- [3] Tanaka A, Matsuda H. Expression of nerve growth factor in itchy skin of atopics Nc/Nga Tnd Mice. *J Med Vet Sci* 2005;67(9):915–9.
- [4] Giannetti A, Fantini F, Cimitan A, Pincelli C. Vasoactive intestinal polypeptide and substance P in the pathogenesis of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1992;176:90–2.
- [5] Toyoda M, Nakamura M, Makino T, Morohashi M. Localization and content of nerve growth factor in peripheral blood eosinophils of atopic dermatitis patients. *Clin Exp Allergy* 2003;33(7):950–5.
- [6] Xiang Z, Nilsson G. IgE receptor-mediated release of nerve growth factor by mast cells. *Clin Exp Allergy* 2000;30(10):1379–86.
- [7] Konishi H, Tsutsui H, Murakami T, Yumikura-Futatsugi S, Yamanaka K, Tanaka M, et al. IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. *Proc Natl Acad Sci USA* 2002;99(17):11340–5.
- [8] Yoshimoto T, Tsutsui H, Tominaga K, Hoshino K, Okamura H, Akira S, et al. IL-18 although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc Natl Acad Sci USA* 1999;96:13962–6.
- [9] Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. *Annu Rev Immunol* 2001;19:423–74.
- [10] Yoshizawa Y, Nomaguchi H, Izaki S, Kitamura K. Serum cytokine levels in atopic dermatitis. *Clin Exp Dermatol* 2002;27(3):225–9.

Olfat G. Shaker*

Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Cairo, Egypt

M. El-Komy

S.O. Tawfic

Department of Dermatology, Faculty of Medicine, Cairo University, Cairo, Egypt

N. Zeidan

R.H. Tomainek

Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt

*Corresponding author. Tel.: +20 127449192

E-mail address: olfatshaker@yahoo.com

(Olfat G. Shaker)

8 February 2008