

FcεRI–FcγRII Coaggregation inhibits IL-16 production from human langerhans-like dendritic cells

By: [Christopher L. Kepley](#), Ke Zhang, Daocheng Zheng, and Andrew Saxon

Kepley, CL, Zhang K, Zhu D, Saxon A. FcεRI–FcγRII coaggregation inhibits IL-16 production from human Langerhans-like dendritic cells. *Clinical Immunology* 2003; 108:89-94.

Made available courtesy of Elsevier: [https://doi.org/10.1016/S1521-6616\(03\)00155-4](https://doi.org/10.1016/S1521-6616(03)00155-4)

***© 2003 Elsevier Inc. Reprinted with permission. This version of the document is not the version of record. Figures and/or pictures may be missing from this format of the document. ***



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](#).

Abstract:

Langerhans-like dendritic cells (LLDC) express the high-affinity IgE receptor FcεRI form that lacks the β-chain, and may play an important role in allergic inflammation via production of IL-16. Secretion of mediators by human mast cells and basophils is mediated through FcεRI and is decreased by coaggregating these receptors to the low-affinity IgG receptor, FcγRII. We used a recently described human Ig fusion protein(GE2), which is composed of key portions of the human γ1 and the human ε heavy chains, to investigate its ability to inhibit IL-16 production from FcεRI-positive Langerhans-like dendritic cells through coaggregation of FcγRII and FcεRI. Unstimulated LLDC-derived from CD14-positive monocytes from atopic donors were shown to express FcγRII, an ITIM-containing receptor, but not FcεRI or FcγRIII which are activating (ITAM) receptors. When passively sensitized with antigen-specific, human IgE and then challenged with antigen, LLDC were stimulated to produce IL-16. However, when FcεRI and FcγRII were coaggregated with GE2, IL-16 production was significantly inhibited. Exposure of LLDCs to GE2 alone did not induce IL-16 production. Our results further extend our studies demonstrating the ability of GE2 to inhibit FcεRI-mediated responses through coaggregation with FcγRIIB and at the same time show that human LDCC can be modulated in a fashion similar to mast cells and basophils.

Keywords: Langerhans cell | Dendritic cells | IgE | Fc receptors | IL-16

Article:

Introduction

Coaggregation of human basophil FcεRI and FcγRII by crosslinking receptor-bound IgE and IgG, respectively, inhibits basophil mediator secretion [1], [2]. We recently showed that a novel human bifunctional Fcε–Fcγ fusion protein (GE2) that binds to FcεRI and FcγRII is capable of inhibiting human FcεRI-α chain, transgenic rodent mast cells, and human basophil functional and

biochemical responses *in vitro* and *in vivo* [3]. In addition to basophils, mast cells, and B cells, Langerhans cells have also been implicated in the afferent and efferent limbs of the allergic response. Thus, epidermal Langerhans cells (LC) are capable of uptake and presentation of allergen-IgE complexes via FcεRI [4]. In addition, crosslinking FcεRI on LC leads to release of IL-16 which participates in allergic inflammation through a variety of mechanisms [5].

Since it is now recognized that β-chain-deficient FcεRI is variably expressed on LC [4], [6], it was important to determine if Langerhans-like dendritic cells (LLDC) also express the inhibitory receptor, FcγRII, as this receptor can inhibit mediator secretion in other cell types. We then examined the hypothesis that the bifunctional GE2, by coaggregating FcγRII with FcεRI, would downregulate important LDC FcεRI-mediated responses.

Here we used LLDC to test the expression of the various FcγRs and to determine if coaggregating FcεRI–FcγRII inhibits their production of IL-16. We demonstrated that these cells express only FcγRII (CD32) and not FcγRI or FcγRIII. We also provide the first evidence that LLDC FcεRI functional responses can be downregulated via FcγRII. Thus, in addition to its ability to block IgE production from human B cells and secretion from human mast cells and basophils, GE2 could also block inflammation through the inhibition of IL-16 production from dendritic cells, another key aspect in the chain of human allergic responses.

Materials and methods

Antibodies and reagents

Anti-FcεRI-α subunit mAb 22E7 was a gift from Dr. J. Kochan. Nonspecific mouse IgG1 (MOPC31C), and antiFcγRIII were from Sigma, (St Louis, MO). The anti-FcγRII mAbs AT10 (IgG1; recognizing all FcγRII isoforms), the anti-FcγRIIIa mAbs IV.3 (IgG1; recognizing FcγRIIIa isoforms), and anti-FcγRI (anti-CD64; clone 32.2, IgG1) Abs were obtained from Medarex (Annendale, NJ). For Western blotting, anti-FcγRIIIa (Ab260)- and FcγRIIb (Ab163)-specific antibodies were obtained from Clark Anderson, (Columbus, OH). The chimeric human anti-4-hydroxy-3-nitrophenacetyl (NP) IgE Abs were from Serotec Ltd. (Oxford, England). To construct the human Fcγ-Fcε protein, the human IgE Fc region was attached to the IgG γ1 constant region using a (Gly₄Ser)₃ flexible linker. The gamma-epsilon fusion protein (GE2) was expressed in cell culture supernatants and purified by using an anti-human IgE affinity column as described [3].

Generation of Langerhans cell-like dendritic cells

Human Langerhans-like dendritic cells were generated from monocytes as described previously [6], [7]. Peripheral blood (100 ml) was obtained from atopic volunteers with approval from the Human Studies Committee at the Medical College of Virginia. Leukocytes were separated from red blood cells by centrifugation over Ficoll-Hypaque (1:1 v/v) at 350g for 20 at room temperature with no break. The leukocyte fraction was washed twice with PBS/BSA and the CD14⁺ monocytes were negatively selected using a kit from Stemcell Technologies as per the manufacture's instructions. The CD14⁺ cells were cultured for 6 days at a cell density of 3.0–10 × 10⁵ cells/ml in culture medium (RPMI 1640 supplemented with 10% heat-inactivated FCS,

10 mM Hepes, 2 mM l-glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin) containing rhIL-4 (100 ng/ml; R&D Systems, Minneapolis, MN), rhGM-CSF (250 ng/ml; Biosource), and natural human TGF-β1 (10 ng/ml; Biosource). NP-specific IgE (1 µg/ml) was added to increase FcεRI expression [6]. Medium was replaced at Days 3–4.

Flow cytometry

Cells were recovered by centrifugation at 800g at 4°C, washed with PBS/BSA, and incubated for 30 min at 4°C with a 1:500 dilution of normal human serum. The cells were washed and incubated with the indicated Abs (10 µg/ml) for 1 h at 4°C. After antibody labeling, the cells were washed and incubated with a 1:100 dilution of F(ab')₂-FITC-goat anti-mouse for 30 min at 4°C. After 3 washes, cells were resuspended in 400 µl of PBS/BSA. The mean intensity fluorescence was determined for at least 10,000 cells using a flow cytometer. MOPC31C was used as negative controls. All experiments were performed in duplicate.

Cell activation

LLDC were suspended in fresh medium (without cytokines) and sensitized with 1 µg/ml of human anti-NP IgE overnight at 37°C in a 5% CO₂ incubator. The next morning, cells were incubated with or without different concentrations of GE2 (0–5 µg/ml), nonspecific IgE (PSIgE; 5 µg/ml), or nonspecific IgG (5 µg/ml) for 2 h. Cells were washed once with HBSS⁻ (Hanks' buffered saline solution without Ca²⁺ or Mg²⁺) [8] and resuspended to 0.5–1.1 × 10⁶ cells/ml in prewarmed HBSS⁺ (HBSS with 1.4 mM CaCl₂ and 1 mM MgCl₂). Washed cells were activated by incubation at 37°C for 12 h with optimal concentrations of NP-BSA (15 µg/ml) at 37°C in a 5% CO₂ incubator followed by centrifugation at 150g at 4°C. Alternatively, GE2 (5 µg/ml) or nonspecific IgE (5 µg/ml) was added for at least 2 h before challenge with varying concentrations of NP-BSA. Supernatants were stored at -70°C. IL-16 was measured in the supernatants using a kit from Biosource, (Camarillo, CA). All experiments were performed in duplicate.

Immunoprecipitation and immunoblotting

IgE-sensitized LLDC, with or without GE2, were activated as above. Preparation of cell lysates, immunoprecipitation, and Western blotting were as previously described [2], [3], [8].

Statistics

IL-16 production in GE2-treated and nontreated cells was compared using the unpaired *t* test with Welch's correction (Graphpad Prism).

Results

LLCC express FcεRI and FcγRII

We initially determined if LLDC expressed various FcγR receptors as potential binding sites for GE2 such that they would allow for coaggregation with FcεRI and subsequent downregulation of

FcεRI-mediated activation. LLDC were generated from purified monocytes by a 6-day culture in IL-4, GM-CSF, and TGF-β1. Confirming previous studies [6], these cells expressed CD1a, E-cadherin, CLA, but not FcγRI or FcγRIII (data not shown). As seen in Fig. 1A, LLDC clearly expressed both FcεRI and FcγRII. Expression of both receptors was detected on greater than 90% of LLDC.

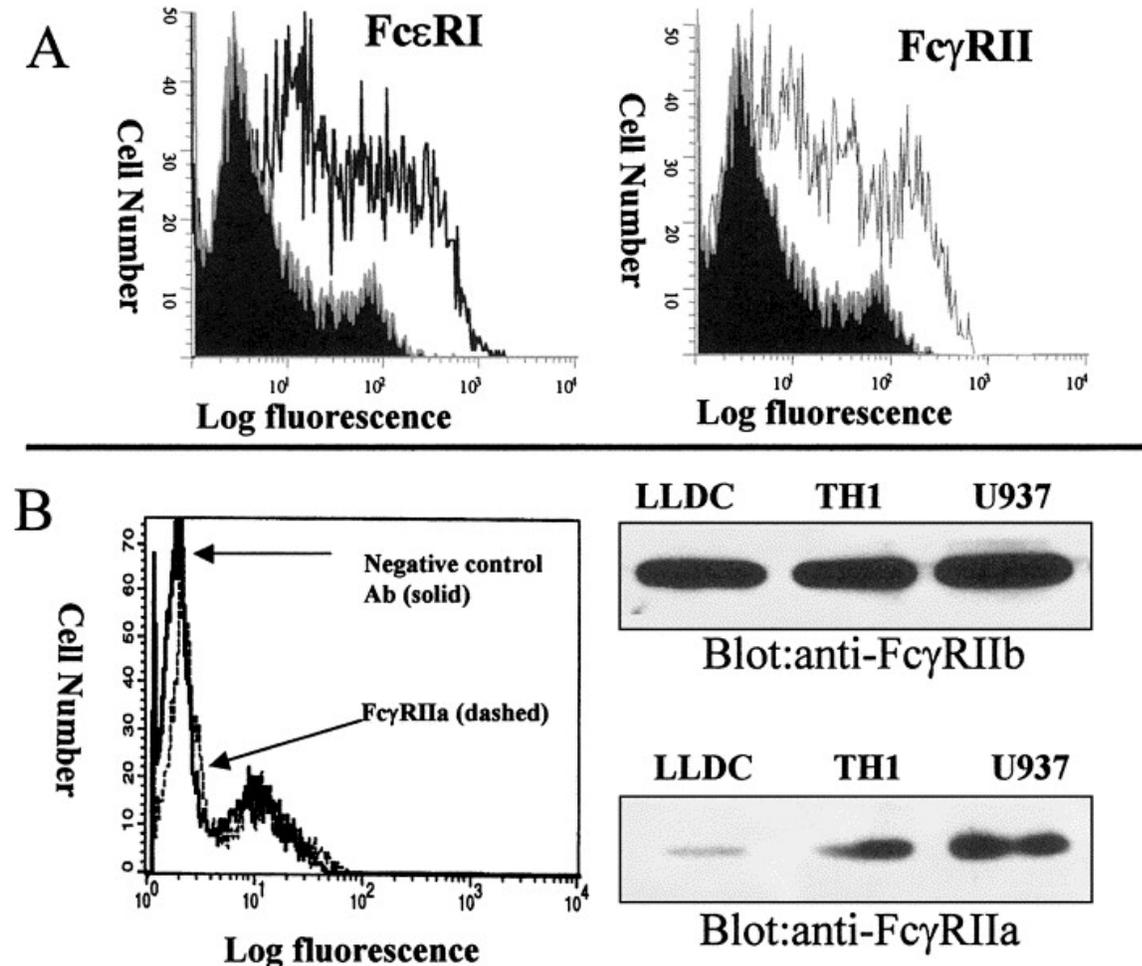


Fig. 1. (A) LLDC express FcεRI and FcγRII. LLDC were incubated at 4°C with 22E7 or AT10 (10 μg/ml) followed by FITC-labeled goat anti-mouse IgG antibodies (unfilled). An irrelevant mouse IgG (MOPC) was substituted for the receptor Abs as a negative control (filled). (B) Lack of expression of FcγRIIa isoforms by LLDC. (Left panel) LLDC were incubated at 4°C with IV.3 (10 μg/ml) followed by FITC-labeled goat anti-mouse IgG antibodies (dashed line). An irrelevant mouse IgG (MOPC) was substituted for the receptor Abs as a negative control (solid line). For Western blotting (right panel), U937 and TH1 cells (as positive controls) or LLDC were lysed, and the clarified supernatants immunoprecipitated with anti-FcγRIIa or anti-FcγRIIb-specific Abs [28]. shows FcγRII immunoprecipitated from 8×10^6 cells. The results are representative of two separate experiments.

There are multiple FcγRII isoforms, representing the products of three distinct genes. Further experiments were performed to investigate which FcγRII receptors are found on LLDC. We detected low expression of FcγRIIa using FACs and Western blotting (Fig. 1B). Thus, although low expression of FcγRIIa was detected, it appears FcγRIIb is the main Fcγ receptor expressed on LLDC.

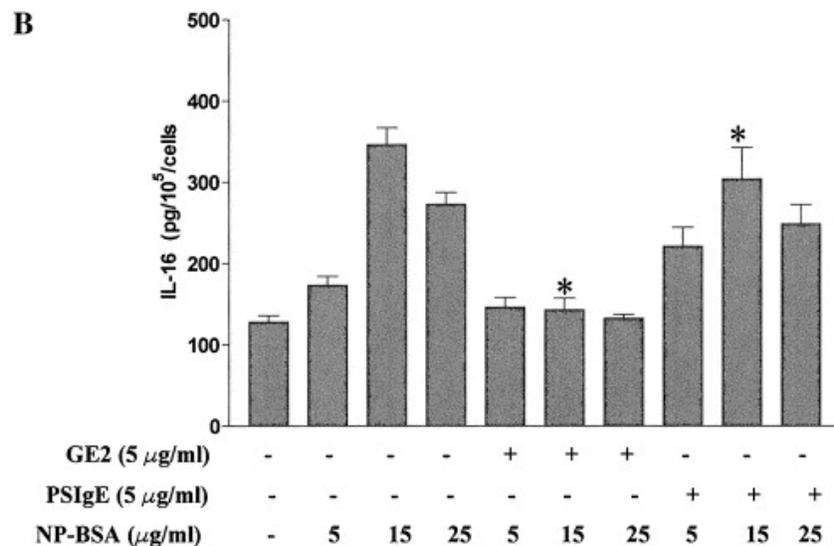
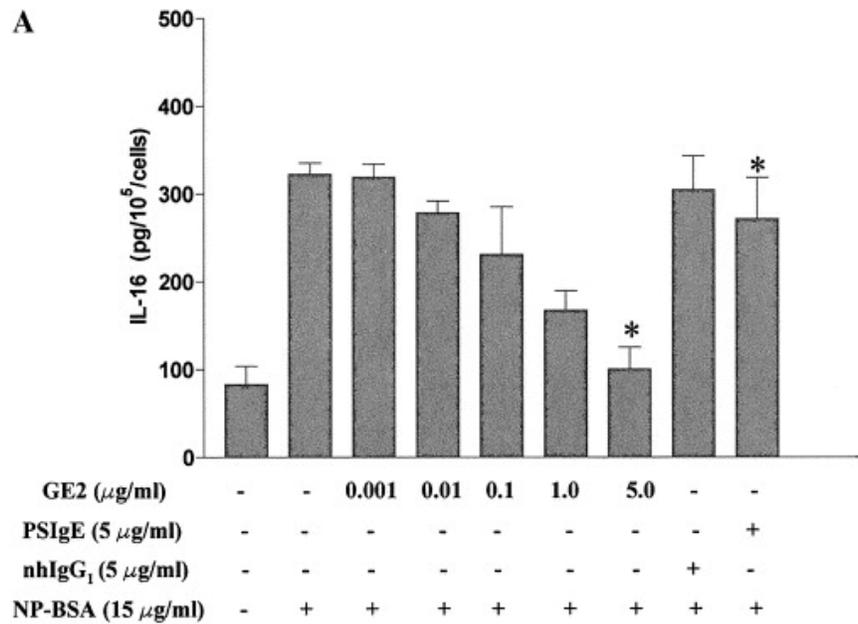


Fig. 2. Fc γ RII/Fc ϵ RI coaggregation inhibits Fc ϵ RI-mediated LLDC IL-16 production. (A) LLDC were incubated with anti-NIP IgE (1 $\mu\text{g/ml}$) for at least 1 day. Cells were washed and incubated with increasing concentrations of GE2, nonspecific IgE (5 $\mu\text{g/ml}$; PS), or nonspecific normal human IgG₁ (5 $\mu\text{g/ml}$; nh) in Iscove's medium at 37°C in a 5% CO₂ incubator. Cells were washed and challenged with 15 $\mu\text{g/ml}$ of NP-BSA for 12 h and the supernatants assayed for IL-16 production. Results from two separate experiments, each done in duplicate, are shown with the standard error of the mean (\pm SEM). *Values significantly reduced ($P < 0.05$) when comparing cells challenged with or without GE2. In B IgE-sensitized cells were incubated for 2 h with GE2 (5 $\mu\text{g/ml}$) or nonspecific PSiGE in Iscove's medium at 37°C in a 5% CO₂ incubator. The cells were washed and incubated with or without varying concentrations of NP-BSA for 12 h, and IL-16 was measured in the supernatants. Results are represented as the standard error of the mean of three separate experiments (\pm SEM). *Values significantly reduced ($P < 0.01$) when comparing cells challenged with or without GE2.

Fc γ RII/Fc ϵ RI coaggregation inhibits LLDC Fc ϵ RI-mediated IL-16 production

Recent studies indicate that IL-16, a potential mediator of allergic disease [5], is released from LLDC after IgE/Fc ϵ RI activation [6]. Given that we had shown that LLDC express Fc ϵ RI and

Fc γ RII, we wanted to examine whether coaggregating these receptors via the GE2 protein could inhibit IL-16 secretion. To test this hypothesis we sensitized LLDC with anti-NIP IgE, treated them with or without GE2, and then activated them with NIP-BSA for 12 h. LDCC secretion of IL-16 in the culture supernatant was then measured. As seen in Fig. 2A, GE2 inhibited IL-16 production in a dose-dependent fashion with a maximal inhibition seen with 5 μ g/ml (63% inhibition). The inhibition of IL-16 secretion was also observed at several concentrations of antigen stimulation. Levels of anti-NIP IgE/NIP-BSA-mediated IL-16 secretion were maximal when LDCC were cultured with 15 μ g/ml NIP-BSA for 12 h (SEM 368 pg/10⁵ cells; \pm 13, n = 3) comparable to previous studies [6]. However, GE2 preincubation reduced the production of IL-16 from LLDC by 47, 64, and 65%, at 5, 15, and 25 μ g/ml antigen, respectively, compared to cells treated with equal amounts of nonspecific human myeloma IgE (Fig. 2B).

Discussion

In this report we demonstrate that Fc ϵ RI-induced IL-16 production on LLDC can be inhibited by coaggregation with Fc γ RII. Because human dendritic cells express Fc ϵ RI, this was very important to demonstrate as the fusion protein GE2 is predicted to interact with these cells in addition to mast cells and basophils.

IL-16 is a homotetramer of 14-kDa subunits and plays a role in allergic inflammation. It is secreted by a wide range of cells including mast cells and airway epithelial cells [5]. This cytokine has been shown to affect many inflammatory mediators such as histamine, regulated upon activation, normal T cells expressed and secreted (RANTES), and monocyte chemoattractant protein-1 (MCP-1) [5]. It is also a potent chemoattractant for CD4⁺ lymphocytes which are important effector cells during the late phase of allergic inflammation. Studies also suggest that IL-16 may contribute to the pathogenesis of allergic asthma through the production of allergen-specific IgE, recruitment of inflammatory cells to the lung, and induction of airway hyperresponsiveness [9], [10], [11]. Preventing its release from cells resident in the skin and lung is likely to be beneficial in the treatment of allergic inflammation, especially in atopic eczema/dermatitis syndrome (AEDS) [12], [13], allergic rhinitis [14], and asthma [11].

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by cutaneous skin lesions containing increased numbers of LC. It is common for children with the disease to develop asthma and/or allergic rhinitis later in life [15]. A link between allergen exposure and AD is suggested based on several observations. First, many AD patients exhibit similar immunological findings as allergic rhinitis and asthma patients including increased serum and allergen-specific IgE [16]. Second, food allergies can exacerbate skin rashes in a subset of patients with AD [17]. Third, AD patients challenged with aeroallergens, either by inhalation or epicutaneously, often develop pruritis and eczematoid skin lesions [18], [19], [20]. Fourth, the LC present in AD skin lesions overexpress Fc ϵ RI which can be activated by IgE-mediated crosslinking and uptake antigen through IgE [21], [22], [23]. Lastly, it has been recently shown that topical exposure to peanut allergen is a risk factor for the development of generalized peanut allergy [24] while epicutaneous sensitization with natural rubber latex induces T helper 2-dominated dermal inflammation and a strong IgE response in a murine model of natural rubber latex-induced, protein contact dermatitis [25]. Therefore, these studies indicate that IgE-Fc ϵ R-

mediated mechanisms may play a role in AD and suggest a link between generalized allergic sensitization and AD.

A current hypothesis proposes that FcεRI on LC is used to present Ag through the uptake of IgE–Ag complexes resulting in allergen-specific T-cell responses that lead to further IgE production and the late-phase response characteristic of delayed-type hypersensitivity (DTH) [21], [22]. Indeed, some AD patients present DTH-like lesions when using the atopy patch test where antigen is injected in the skin [26]. However, similar to LC, human mast cells express MHC class II, can present antigen, and activate CD4+ T cells [27]. Thus, it is not clear what mechanisms lead to the characteristic recruitment of T cells into AD lesions. Nonetheless, GE2 could potentially interfere with the uptake of IgE antigen by blocking FcεRI antigen presentation capabilities. We are currently investigating this hypothesis.

Initially we showed that the human bifunctional Fcε–Fcγ fusion was capable of inhibiting in vivo rodent mast cell and in vitro human basophil functional responses [3]. Subsequently, we have demonstrated that GE2 can specifically inhibit IgE production by human B cells (Yamada et al., *J. Biol. Chem.*, in press) as well as functional and biochemical responses from human mast cells (Kepley et al., submitted). We have now shown that this approach using the Fc domain of IgE to target and downregulate inflammatory mediator release from FcεRI-positive cells may have beneficial effects on later phases of allergic responses-mediated cells other than mast cells and basophils. This finding increases the potential of GE2 to be used therapeutically in the treatment of human allergic disorders.

Acknowledgements

This work was supported by a NIH grant (AI-15251). C.L.K. was also supported by an Interest Section grant from the American Academy of Allergy Asthma and Immunology, a Research Grant from the American Lung Association, and a Fellowship from the Parker B. Francis Foundation.

References

- [1] M. Daeron, S. Latour, O. Malbec, E. Espinosa, P. Pina, S. Pasmans, W.H. Fridman, The same tyrosine-based inhibition motif, in the intracytoplasmic domain of Fc gamma RIIB, regulates negatively BCR-, TCR-, and FcR-dependent cell activation, *Immunity* 3 (1995) 635–646.
- [2] C.L. Kepley, J.C. Cambier, P.A. Morel, D. Lujan, E. Ortega, J.M. Oliver, Negative regulation of FcεRI signaling by FcγRII costimulation in human blood basophils, *J Allergy Clin Immunol.* 106 (2000) 337–348.
- [3] D. Zhu, C.L. Kepley, M. Zhang, K. Zhang, A. Saxon, A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation, *Nature Med.* 8 (2002) 518–521.

- [4] K. Ochiai, B. Wang, A. Rieger, O. Kilgus, D. Maurer, D. Fodinger, J.P. Kinet, G. Stingl, H. Tomioka, A review on Fc epsilon RI on human epidermal Langerhans cells, *Int. Arch. Allergy Immunol.* 104 (1994) 63–64.
- [5] P. Conti, D. Kempuraj, K. Kandere, M. Di Gioacchino, M. Reale, R.C. Barbacane, M.L. Castellani, U. Mortari, W. Boucher, R. Letourneau, T.C. Theoharides, Interleukin-16 network in inflammation and allergy, *Allergy Asthma Proc.* 23 (2002) 103–108.
- [6] K. Reich, A. Heine, S. Hugo, V. Blaschke, P. Middel, A. Kaser, H. Tilg, S. Blaschke, C. Gutgesell, C. Neumann, Engagement of the Fc epsilon RI stimulates the production of IL-16 in Langerhans cell-like dendritic cells, *J. Immunol.* 167 (2001) 6321–6329.
- [7] F. Geissmann, C. Prost, J.P. Monnet, M. Dy, N. Brousse, O. Hermine, Transforming growth factor beta 1, in the presence of granulocyte/macrophage colony-stimulating factor and interleukin 4, induces differentiation of human peripheral blood monocytes into dendritic Langerhans cells, *J. Exp. Med.* 187 (1998) 961–966.
- [8] C.L. Kepley, B.W. Wilson, J.M. Oliver, Identification of the Fc epsilon RI-activated tyrosine kinases Lyn, Syk, and Zap-70 in human basophils, *J. Allergy Clin. Immunol.* 102 (1998) 304–315.
- [9] W.W. Cruikshank, A. Long, R.E. Tarpy, H. Kornfeld, M.P. Carroll, L. Teran, S.T. Holgate, D.M. Center, Early identification of interleukin-16 (lymphocyte chemoattractant factor) and macrophage inflammatory protein 1 alpha (MIP1 alpha) in bronchoalveolar lavage fluid of antigen-challenged asthmatics, *Am. J. Respir. Cell. & Mol. Biol.* 13 (1995) 738–747.
- [10] E.M. Hessel, W.W. Cruikshank, A. Van, J.J. De Bie, B. Van Esch, G. Hofman, F.P. Nijkamp, D.M. Center, A.J. Van Oosterhout, Involvement of IL-16 in the induction of airway hyper-responsiveness and up-regulation of IgE in a murine model of allergic asthma, *J. Immunol.* 160 (1998) 2998–3005.
- [11] R.A. Taha, S. Laberge, Q. Hamid, R. Olivenstein, Increased expression of the chemoattractant cytokines eotaxin, monocyte chemoattractant protein-4, and interleukin-16 in induced sputum in asthmatic patients, *Chest* 120 (2001) 595–601.
- [12] A. Frezzolini, M. Paradisi, A. Zaffiro, A. Provini, S. Cadoni, M. Ruffelli, O. De Pita, Circulating interleukin 16 (IL-16) in children with atopic/eczema dermatitis syndrome (AEDS): a novel serological marker of disease activity, *Allergy* 57 (2002) 815–820.
- [13] K. Reich, S. Hugo, P. Middel, V. Blaschke, A. Heine, C. Gutgesell, R. Williams, C. Neumann, Evidence for a role of Langerhans cell-derived IL-16 in atopic dermatitis, *J. Allergy Clin. Immunol.* 109 (2002) 681–687.
- [14] T. Pullerits, A. Linden, C. Malmhall, J. Lotvall, Effect of seasonal allergen exposure on mucosal IL-16 and CD4₊ cells in patients with allergic rhinitis, *Allergy* 56 (2001) 871–877.

- [15] D.Y. Leung, Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases, *J. Allergy Clin. Immunol.* 96 (1995) 302–318.
- [16] D.Y. Leung, Pathogenesis of atopic dermatitis, *J. Allergy Clin. Immunol.* 104 (1999) S99–108.
- [17] S.M. Jones, H.A. Sampson, The role of allergens in atopic dermatitis, *Clin. Rev. Allergy* 11 (1993) 471–490.
- [18] R.A. Tupker, J.G. de Monchy, P.J. Coenraads, A. Homan, J.B. van der Meer, Induction of atopic dermatitis by inhalation of house dust mite, *J. Allergy Clin. Immunol.* 97 (1996) 1064–1070.
- [19] E.B. Mitchell, J. Crow, G. Williams, T.A. Platts-Mills, Increase in skin mast cells following chronic house dust mite exposure, *Br. J. Dermatol.* 114 (1986) 65–73.
- [20] S. Reitamo, K. Visa, K. Ka`yhko`nen, K. Ka`yhko, S. Stubb, O.P. Salo, Eczematous reactions in atopic patients caused by epicutaneous testing with inhalant allergens, *Br. J. Dermatol.* 114 (1986) 303–309.
- [21] G.C. Mudde, F.C. Van Reijssen, G.J. Boland, G.C. de Gast, P.L. Bruijnzeel, C.A. Bruijnzeel-Koomen, Allergen presentation by epidermal Langerhans' cells from patients with atopic dermatitis is mediated by IgE, *Immunology* 69 (1990) 335–341.
- [22] N. Novak, S. Kraft, T. Bieber, Unraveling the mission of FcεRI on antigen-presenting cells, *J. Allergy Clin. Immunol.* 111 (2003) 38–44.
- [23] M. Jurgens, A. Wollenberg, D. Hanau, de la, H. Salle, T. Bieber, Activation of human epidermal Langerhans cells by engagement of the high affinity receptor for IgE, Fc εRI. *J. Immunol.* 155, (1995) 5184–5189.
- [24] G. Lack, D. Fox, K. Northstone, J. Golding, Factors associated with the development of peanut allergy in childhood, *N. Engl. J. Med.* 348 (2003) 977–985.
- [25] M. Lehto, M. Koivuluhta, G. Wang, I. Amghaiab, M.L. Majuri, K. Savolainen, K. Turjanmaa, H. Wolff, T. Reunala, A. Lauerma, T. Palosuo, H. Alenius, Epicutaneous natural rubber latex sensitization induces T helper 2-type dermatitis and strong prohevein-specific IgE response, *J. Invest Dermatol.* 120 (2003) 633–640.
- [26] E.G. Langeveld-Wildschut, P.L. Bruijnzeel, G.C. Mudde, C. Versluis, A.G. Van Ieperen-Van Dijk, I.C. Bihari, E.F. Knol, T. Thepen, C.A. Bruijnzeel-Koomen, F.C. Van Reijssen, Clinical and immunologic variables in skin of patients with atopic eczema and either positive or negative atopy patch test reactions, *J. Allergy Clin. Immunol.* 105 (2000) 1008–1016.

[27] P. Poncet, M. Arock, B. David, MHC class II-dependent activation of CD4⁺ T cell hybridomas by human mast cells through superantigen presentation, *J. Leukocyte Biol.* 66 (1999) 105–112.

[28] S. Tridandapani, K. Siefker, J-L. Teillaud, J. Carter, M. wewers, C. Anderson, Regulated expression and inhibitory function of Fc γ RIIb in human monocytes, *J. Biol. Chem.* 277 (2002) 5082–5089.