

Topical application of PPAR α (but not β/δ or γ) suppresses atopic dermatitis in NC/Nga mice

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Abstract

Background: Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors, which regulate not only adipogenesis and proliferation/differentiation but also the immune response of cells. Because topical application of the activators of some PPAR isoforms improved clinical symptoms in patients with atopic dermatitis (AD), we investigated the role of PPAR activators using a murine AD model in NC/Nga mice; to the best of our knowledge, this has not been previously reported.

Methods: Activators of three PPAR isoforms (α , β/δ , γ) were topically applied on inflamed skin in a murine AD model that was developed by repeated topical application of mite antigen in NC/Nga mice. The efficacy of each topical PPAR activator was evaluated immunologically and serologically.

Results: Topical application of the PPAR α activator, but not of the activators of PPAR β/δ or PPAR γ , improved clinical dermatitis, reduced inflammatory cell infiltration in the dermis, and alleviated the elevation of serum IgE levels. In addition, PPAR α expression was downregulated in the epidermis in our murine AD model, as is seen in patients with AD.

Conclusions: Topical application of PPAR α activator could be a potent therapeutic agent for patients with AD and could take the place of topical steroid treatments.

Atopic dermatitis (AD) is a chronic and relapsing skin disease, histopathologically characterized by the selective accumulation of inflammatory cells (1, 2). The skin inflammation is thought to result partly from a complicated interaction between altered keratinocytes and activated Th2 lymphocytes, eosinophils, and mast cells. Moreover, chronic persistent inflammation causes deterioration of the epidermal functions of protection, moisture retention, and antimicrobial defense (3, 4). Although immunological or hereditary abnormalities in AD have become clear in recent years, topical glucocorticoid application is still the most effective therapy and is the standard treatment in many guidelines (5, 6). Prolonged use of topical glucocorticoids could result in long-term risks such as telangiectatic lesions, cutaneous atrophy, and steroid acne (7). Therefore, there is a need for more effective alternative therapies without negative side-effects.

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily of ligand-activated transcription factors. Peroxisome proliferator-activated receptors promote the expression of target genes by forming heterodimers with retinoid X receptor (RXR)

and binding to specific motifs known as PPAR-responsive elements (8). To date, three mammalian PPAR subtypes encoded by separate genes have been identified, namely α , β (also termed δ), and γ . Among these, PPAR α and high levels of PPAR γ are expressed in adipocytes and play key roles in regulating insulin sensitization and adipogenesis (9, 10). In recent years, it has been reported that PPAR α and γ have substantial anti-inflammatory activity in murine models of both irritant and acute allergic contact dermatitis. Topical activators of PPAR α or systemic PPAR γ ligation have been shown to reverse clinical dermatosis and improve barrier function in acute allergic contact dermatitis murine models (11, 12). Tissue eosinophil activation is one of the hallmarks of allergic diseases, including AD. We previously showed that the stimulation of eosinophils with a synthetic PPAR γ agonist inhibited factor-induced eosinophil activation (13, 14). Therefore, evidence suggests that targeting PPAR α or PPAR γ may be a new therapeutic approach in the treatment of AD.

In this study, we evaluated the effect of several PPAR activators in a murine model of AD, developed by repeated

application of *Dermatophagoides farinae* (Df) extract ointment in NC/Nga mice (15). Our data show that the PPAR α activator regulates epidermal thickening and inflammatory cell infiltration into the dermis in this murine model. Interestingly, the pattern of epidermal PPAR α expression in the Df-induced NC/Nga murine AD-like model was similar to that seen in the skin lesions of patients with AD.

Methods

Animals and materials

NC/Nga mice (female mice; age, 8–9 weeks) were obtained from Charles River Laboratories (Tokyo, Japan) and were maintained in specific pathogen-free conditions. The protocol was approved by the Committee of Ethics on Animal Experiments in the Graduate School of Medical Sciences, Kyushu University. WY14643 (PPAR α agonist), GW0742 (PPAR β/δ agonist), and ciglitazone (PPAR γ agonist) were purchased from Cayman Chemicals (Ann Arbor, MI, USA), and their molecular weights were 323.8, 471.5, and 333.4, and solubilities in ethanol were approximately 16.5, 25, and 16 mg/ml, respectively. Betamethasone valerate (BV), propylene glycol, and ethanol were obtained from Sigma (St. Louis, MO, USA). Biostir reagent (*D. farinae* body [Dfb] ointment) was prepared by Biostir Inc (Tokyo, Japan). One gram of Dfb ointment contained 136.4 mg protein, 234 μ g Der f 1, and 7 μ g Der f 2.

Induction of AD-like skin lesions and topical application of PPAR agonists in NC/Nga mice

On day 0, the hair on the backs of mice was clipped using an electric clipper and residual hair was epilated by using a hair removal cream. On day 1, barrier disruption was effected by the application of 100 μ l of 4% sodium dodecyl sulfate (Sigma) on the dorsal shaved skin; antigen challenge was then performed by the topical application of 100 mg Biostir reagent. These procedures were repeated twice a week. After nine challenges (4 weeks), AD-like chronic dermatitis was established (15). The NC/Nga mice were equally divided into six groups (vehicle alone [propylene glycol/ethanol, 7 : 3], Biostir alone, Biostir plus WY14643, Biostir plus GW0742, Biostir plus ciglitazone, and Biostir plus 0.2% BV dissolved in vehicle). The concentration of each PPAR agonist was adjusted to 10 mM in the vehicle (propylene glycol/ethanol, 7 : 3). The topical application of 200 μ l of the PPAR agonist or BV was performed once every day for three additional weeks after the first two challenges. During the 21 days after first two challenges, 3600 μ l of the PPAR agonist or BV was applied to each mouse in total. The painted back skin and blood samples were collected immediately afterward for histological and serological analyses.

Histopathological analysis for skin inflammation

The back skin samples were fixed in 4% phosphate-buffered formalin solution, mounted in paraffin, sliced into 3- μ m-

thick sections, and stained with hematoxylin–eosin or with toluidine blue for mast cells. Epidermal thickness was determined at 400-fold magnification using an ocular micrometer; an average of five measures was calculated for each sample. To assess the number of dermal infiltrating cells, eosinophils, and mast cells, five high power fields (HPFs) per skin section from each mouse were randomly selected, the cell numbers per field were counted, and the mean cell numbers determined. Some skin samples were sliced into 6- μ m-thick sections and prepared on slides. The sections were dewaxed in xylene, rehydrated through a graded series of ethanol solutions, and then immersed in methanol with 0.3% hydrogen peroxide for 30 min. The slides were blocked with 10% goat serum at room temperature for 10 min and incubated at 4°C overnight in Tris-buffered saline containing rabbit polyclonal antibodies against either PPAR α (1 : 50) or PPAR γ (1 : 200) (LifeSpan Biosciences Inc, Seattle, WA, USA). Then, sections were incubated with the secondary antibody for 30 min. Positive reactions were identified using peroxidase-conjugated streptavidin and DAB enhancer (Dako, Glostrup, Denmark).

Real-time reverse transcriptase-polymerase chain reaction analysis

The back skin from each mouse was excised, immediately frozen in dry ice, and total RNA extracted using the RNeasy kit (Qiagen, Valencia, CA, USA). Extracted RNA (2 μ g) was reverse transcribed using a PrimeScriptTM RT Reagent kit (Takara Bio Inc., Shiga, Japan) in a total volume of 10 μ l. Quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) was performed on an Mx3000p system (Stratagene, La Jolla, CA, USA) using SYBR[®] Premix Ex TaqTM (Takara Bio Inc.). The primers, purchased from Takara Bio Inc. and SABiosciences (Frederick, MD, USA), were as follows: glyceraldehyde-3-phosphate (GAPDH), 5'-TGTGTCCGTCGTGGATCTGA-3' and 5'-TTGCTGTGAAGTCGCAGGAG-3'; and PPAR α , 5'-AAGTGCCTGTCTGTCGGGATG-3' and 5'-CCAGAGATTTGAGGTCTGCAGTTTC-3'. Amplification was performed at the following temperature cycling conditions: initial denaturation at 95°C for 10 s followed by 40 cycles at 95°C for 5 s and 60°C for 20 s, successively. The amount of mRNA of the target gene was normalized to that of GAPDH using the ΔC_t method, as described in the manufacturer's protocol.

Measurements of serum IgE and thymus and activated-related chemokine

Blood samples were collected from mouse hearts at the end of the therapeutic protocol described above. Serum IgE and thymus and activation-related chemokine (TARC) concentrations were measured by enzyme-linked immunosorbent assays using mouse IgE quantitation kit (Genway, San Diego, CA, USA) and Quantikine immunoassay for mouse CCL17/TARC (R&D systems, Minneapolis, MN, USA), respectively, according to the manufacturers' instructions.

Statistical analysis

Data are presented in terms of mean and standard deviations (SD). A one-way analysis of variance with repeated measures was used for the comparison of more than two variables. When the initial P value was <0.05 , Scheffe's test was used to determine the significance between groups. Significance was established at P values < 0.05 .

Results

PPAR α agonist impairs skin inflammatory response in murine AD model

We initially investigated the effect of PPAR agonists on the skin inflammatory response in the Biostir-induced AD mouse model. In line with a previous study (15), Biostir/vehicle treat-

ment clinically induced AD-like skin lesions such as edema, scratch mark, and lichenification in mice. Treatment with the PPAR α agonist as well as with the glucocorticoid BV, but not with the PPAR β/δ or PPAR γ agonists, ameliorated these symptoms (Fig. 1A). The clinical response to these agonists was reflected in the histopathology. Mice treated with Biostir/vehicle showed epidermal thickening and dense inflammatory cell infiltration (Fig. 1B); this epidermal thickness was reduced by 64% ($P < 0.05$) in mice treated with the PPAR α agonist (Fig. 1C). On the other hand, epidermal thickening tended to be high in mice treated with the PPAR β/δ agonist.

PPAR α agonist causes a decrease in inflammatory cell accumulation in murine AD model

We also investigated general inflammatory indicators (total inflammatory cell infiltration, tissue eosinophilia, and mast

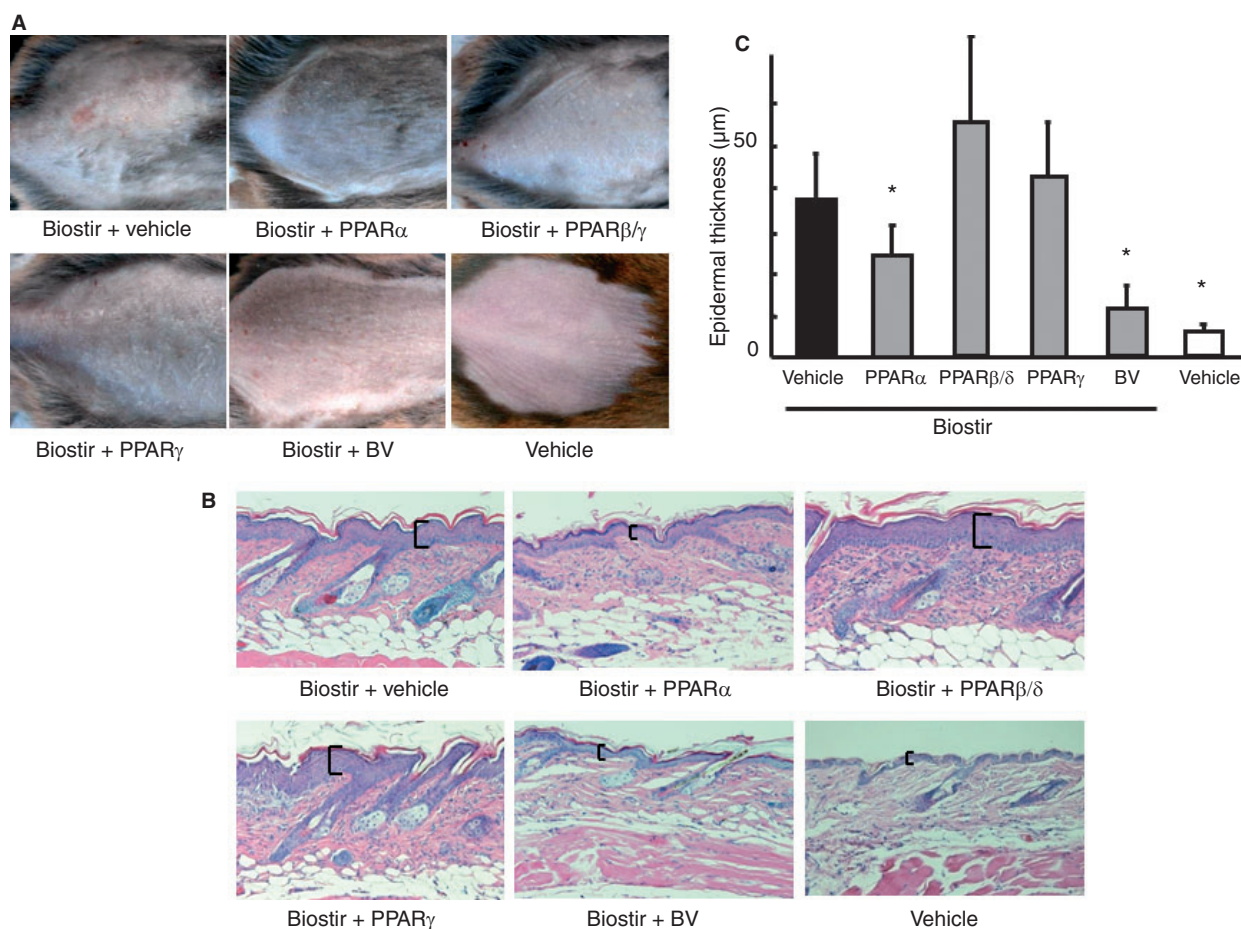


Figure 1 (A) Photographs of the clinical features of NC/Nga mice treated with Biostir plus vehicle, Biostir plus peroxisome proliferator-activated receptor (PPAR) α agonist (10 mM WY14643), Biostir plus PPAR β/δ agonist (10 mM GW0742), Biostir plus PPAR γ agonist (10 mM ciglitazone), Biostir plus 0.2% betamethasone valerate (BV), and the vehicle alone (untreated) on day 28 following the first challenge. (B) Histological appearance after treatment with each

agonist or with BV (hematoxylin and eosin staining; 200 $\times$ magnification). (C) Quantitative change in epidermal thickening after treatment with each agonist or with BV. Average epidermal thickness was assessed from randomized micrographs (see the Methods section). Data are expressed as mean $\pm$ standard deviation (SD). * $P < 0.05$ vs Biostir plus vehicle; $n = 5$.

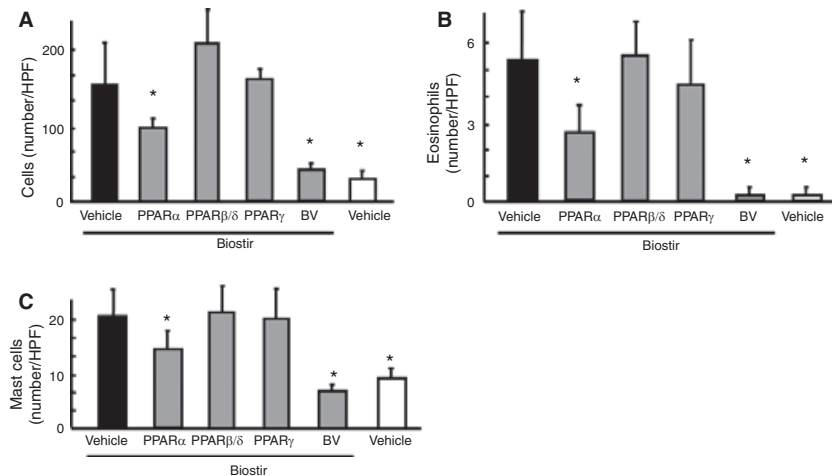


Figure 2 (A) Total inflammatory cell counts (per high power field [HPF]) were quantified as described in the Methods section. (B), (C) Quantitation of tissue eosinophils and mast cell numbers was

cell density). Treatment with PPAR α agonist and potent topical glucocorticoid BV caused a significant decrease in inflammatory cell infiltration (Fig. 2A), tissue eosinophilia (Fig. 2B), and mast cell density (Fig. 2C); these effects were not seen in the mice treated with PPAR β/δ or PPAR γ agonists.

PPAR α agonist prevents the increase in serum IgE level in murine AD model

Total serum IgE levels at the end of the therapeutic protocol were lower in mice treated with the PPAR α agonist than in those treated with Biostir/vehicle (Fig. 3A). However, treatment with PPAR α agonist did not prevent the increase in serum TARC levels in the murine AD model (Fig. 3B). Treatment with PPAR β/δ or PPAR γ agonists did not have significant effects on either serum IgE or TARC levels.

PPAR α expression is decreased in the lesional skin of murine AD model

Next, to evaluate the mechanism of therapeutic effects of the PPAR α agonist, we investigated whether PPAR expression is

performed as described in the Methods section. These data are expressed as mean $\pm$ standard deviation (SD). * $P < 0.05$ vs Biostir plus vehicle; $n = 5$.

modulated on the lesional back skin of AD mice. As shown in Fig. 4A, PPAR α was poorly expressed in AD mice when compared to normal mice (vehicle alone). However, PPAR γ expression was similar in both AD and normal mice. To further investigate PPAR α expression, we measured PPAR α mRNA expression using quantitative RT-PCR. The expression of PPAR α mRNA was lower in AD mice than in normal mice. Interestingly, treatment with PPAR α agonist or BV reversed this observed downregulation of PPAR α mRNA (Fig. 4B).

Discussion

To the best of our knowledge, we showed for the first time the anti-inflammatory role of a PPAR α agonist in a murine AD model developed by repeatedly applying Df extracts. Previously, a topical PPAR α agonist was shown to inhibit epidermal hyperplasia and inflammatory cell infiltration in a murine model of chronic allergic dermatitis caused by repeated topical application of ovalbumin (16). Treatment with the PPAR α agonist WY14643 successfully reduced skin expressions of interleukin (IL)-4, IL-31, IL-1 β , and eotaxin in this model (16). In addition, Hatano et al. (11) showed that

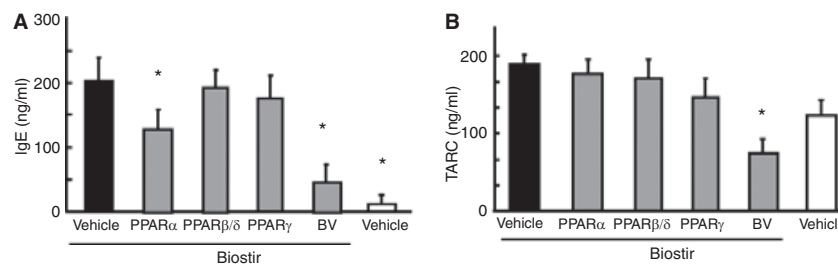


Figure 3 (A) Serum levels of IgE on day 28 following the first challenge. (B) Serum levels of thymus and activation-related chemokine (TARC) on day 28 following the first challenge. These data are

expressed as mean $\pm$ standard deviation (SD). * $P < 0.05$ vs Biostir plus vehicle; $n = 5$.

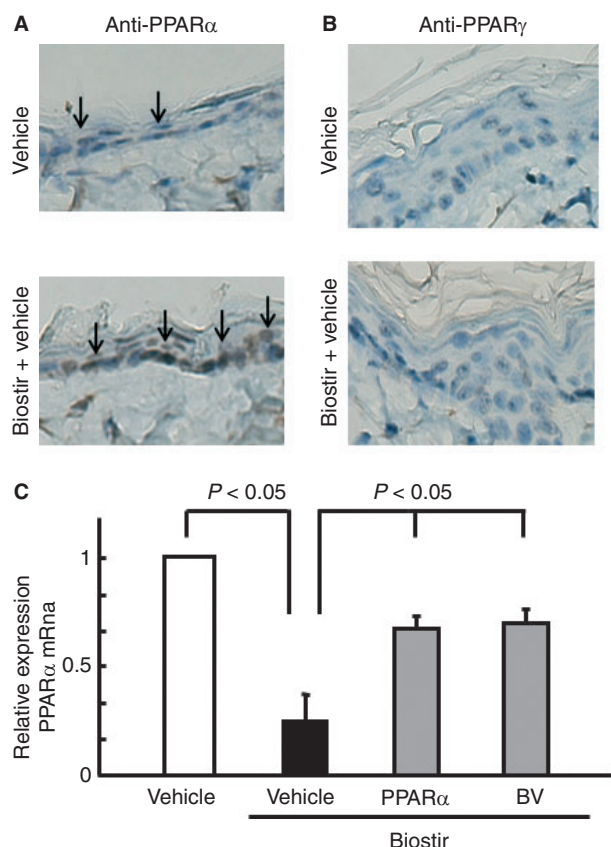


Figure 4 (A) Histological analysis of peroxisome proliferator-activated receptor (PPAR) α expression in the epidermal layer. Black arrows indicate PPAR α -positive cells in the epidermis (original magnification, 400 $\times$). (B) Histological analysis of PPAR γ expression in the epidermal layer (original magnification, 400 $\times$). (C) Relative mRNA expression levels of PPAR α in the skin. Data are expressed as mean $\pm$ standard deviation (SD) of five mice.

treatment with a PPAR α activator attenuated clinical dermatitis, and in particular, improved barrier function in another chronic allergic dermatitis murine model induced by repeated topical application of oxazolone. Peroxisome proliferator-activated receptors α activation also reversed the increase in eosinophils and mast cells in the skin of mouse, in addition to decreasing serum TARC levels (11). The NC/Nga mice used in the present study developed eczema when maintained in conventional conditions, but not when maintained in specific pathogen-free conditions (17). These clinical features and an overproduction of IgE, including a high titer of IgE specific to mite antigen, were similar to those seen in patients with AD. Our findings suggest that topical application of a PPAR α activator potentially regulates antigen-induced skin inflammation in murine AD model, which is similar in pathology to that seen in patients with AD.

Peroxisome proliferator-activated receptors α was initially identified as a transcriptional regulator of key enzymes associated with fatty acid metabolism (18). Peroxisome proliferator-activated receptors α expression is detected in a variety of

cells such as liver, heart, kidneys, muscles, and brown fat (19). Peroxisome proliferator-activated receptors α is also expressed in rodent and human keratinocytes and cutaneous immune cells, particularly Langerhans cells, T lymphocytes, and eosinophils involved in cutaneous allergic dermatitis (20). Studies using selective agonists and knockout mice for PPAR α have shown that PPAR α inactivation decreases the expression of involucrin, which is important for the formation of the corneous layer and activates eosinophil chemotaxis and the nuclear factor kappa B pathway (16, 21, 22). Thus, the anti-inflammatory effects of topical PPAR α agonist application in skin might be directly derived from a reduction in inflammatory cell infiltration and downregulation of inflammatory cytokines.

Contrary to the expectations, topical treatment with ciglitazone, a selective PPAR γ agonist, did not prevent clinical dermatitis or ameliorate inflammatory cell infiltration. Peroxisome proliferator-activated receptors γ is expressed in keratinocytes, Langerhans cells, T lymphocytes, and eosinophils, which are associated with cell differentiation or apoptosis (18, 23, 24). Furthermore, ligand activation of PPAR γ is shown to be associated with multiple inflammatory processes and results in anti-inflammatory effects similar to those seen with PPAR α activation. In fact, systemic application of a PPAR γ activator led to reduced onset of eczematous skin lesions in an AD-like murine model (12). Furthermore, we previously showed that PPAR γ agonist troglitazone reduced IL-5-stimulated eosinophil survival, eotaxin-directed eosinophil chemotaxis, and functional augmentation of eosinophil adhesion in a concentration-dependent manner (14, 25). However, neither our results nor those of Hatano et al. (11) showed anti-inflammatory effects *in vivo*, in spite of previous reports showing similar results *in vitro*. Treatment with a PPAR α agonist, but not with a PPAR γ agonist, decreased antigen-induced skin inflammation in the AD model even though the molecular weights of these reagents were similar (~300 Da). Furthermore, we investigated the differences in mechanisms that led to the failure of the PPAR γ activator to inhibit skin inflammation. Because it has been shown that PPAR α expression is significantly downregulated in the lesional skin of patients with AD (16), we investigated whether PPAR α expression is downregulated in the epidermis of AD mice. Interestingly, we observed a markedly decreased expression of PPAR α in the eczematous skin of AD mice, similar to that observed in patients with AD. To our knowledge, this is the first study showing similar PPAR α expression in the lesional skin of AD mice as that in patients with AD. Furthermore, PPAR α expression in the epidermis increased in conjunction with amelioration of symptoms of cutaneous inflammation. Our study provides additional information about pathological conditions in mouse AD model.

Taken together, our study results show that PPAR α expression is downregulated in inflamed skin of AD model mice, similar to that in patients with AD. Whether this downregulation of PPAR α leads to the development of AD or whether it is a consequence of skin inflammation is yet to be determined. It has been shown that PPAR α mRNA expression is downregulated 6 h after skin barrier damage

caused by topical application of the irritant agent sodium lauryl sulfate (26). Although both PPAR α and PPAR γ have anti-inflammatory effects *in vitro*, topical application of a PPAR γ activator fails to prevent skin inflammation in several mouse models of AD. Thus, it is most likely that a homeostatic effect of PPAR α in epidermal cells may play an important regulatory role in skin inflammation. For example, it has been reported that PPAR α -deficient mice show poor wound healing than that in wild-type mice (27). The PPAR α agonist WY14643 has been shown to inhibit the ultraviolet B light-mediated expression of the inflammatory cytokines IL-6 and IL-8 in human keratinocyte cell line (28). In addition, PPAR α activation has been shown to increase the expression of ATP-binding cassette subfamily A (ABCA) 1, a membrane transporter responsible for cholesterol efflux associated with barrier formation, in cultured human keratinocytes (29). These results suggest that PPAR α in keratinocytes might independently exert a potent immunoregulatory effect *in vivo*, and that the downregulation of PPAR α expression is not only a consequence of skin inflammation.

In summary, we showed that PPAR α agonist ameliorates epidermal hyperplasia, dermal inflammatory cell infiltration, and elevation of serum IgE levels in murine AD model. It is

possible that PPAR α in epidermal cells exerts anti-inflammatory effects in this murine AD model. These findings suggest that a topical PPAR α agonist might be a potential therapeutic modality in inflammatory skin diseases such as AD. Furthermore, we showed significantly reduced PPAR α expression in eczematous skin of AD mice, similar to that in patients with AD. This finding shows that the use of Df-induced NC/Nga AD-like model is appropriate in studies for developing a novel curative therapy for AD. In fact, topical application of a natural PPAR α activator, sunflower oleodistillate, has shown to exert effects similar to those of topical steroids in children with AD (30). However, further studies are required to examine the *in vivo* modulation and collateral effects of PPAR α before its use in clinical applications.

Acknowledgments

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Conflict of interest

None.

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