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Peroxisome Proliferator-Activated Receptors (PPARs) Activation as Therapeutic Targets in Skin Inflammation

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are fatty acid activated transcription factors that belong to the nuclear hormone receptor family. They are initially known as transcriptional regulators of lipid and glucose metabolism, although further evidence has also been accumulated for other functions. Due to the nature of all PPAR isotypes which are expressed and exert effects by regulating the functions of cell types residing and infiltrating in the skin, PPARs represent a major research target for the understanding and treatment of many skin diseases. Atopic dermatitis (AD) is a chronic and relapsing disease characterized by skin barrier dysfunction and immune dysregulation. Skin barrier disturbance is one of the exacerbation factors of AD, due to facile penetration of molecules such as antigens. From the aspect of immune dysregulation, innate and acquired immunity including cell proliferation, cell differentiation, and cytokine network are involved in the pathogenesis. In this review, the role of PPAR in AD and the possibility of its agonist for the treatment of AD are discussed.

Keywords: Peroxisome Proliferator-activated Receptors; Skin; Inflammation; Atopic Dermatitis

1. Introduction

PPARs are classified three different isoforms termed PPARα, PPARβ/δ and PPARγ[1,2]. Initial studies demonstrated that PPARs are pivotal participants in the regulation of energy homeostasis by modulating glucose and lipid metabolism and transportation[3], and then subsequent studies have shown that PPARs regulate in other cellular functions such as cell proliferation, cell differentiation, apoptosis and inflammation. Because all PPAR isotypes are expressed[4] and exert effects by regulating the functions of cell types residing and infiltrating in skin, PPARs represent a major research target for the understanding and treatment of many skin diseases. Atopic dermatitis (AD) is a chronic and relapsing disease. AD is characterized skin barrier dysfunction and immune dysregulation. A typical characteristic of AD is xerosis which affects lesional and non-lesional skin areas, due to increased transepidermal water loss. This skin barrier disturbance exacerbates AD, due to facile penetration of high molecules such as antigens[5]. Thus, the application of emollients is one of the basic treatments to support skin barrier function and allow hydration of the skin as conservative treatments [6]. Immune dysregulation occurs in both innate immunity and acquired immunity. The innate immunity is presented in the epidermis as the front line defense against infection. Antimicrobial peptides (AMPs), directly kill a broad spectrum of microbes, are secreted from keratinocytes and activated to respond immediately after microbial invasion. Although it is supposed that AD patients have a higher prevalence of infection with bacteria, fungi, and viruses due to skin barrier disruption, the defects of innate immune system are demonstrated previously [7]. Regarding dysregulation of acquired immunity, AD is originally regarded as a Th2-mediated disease because of the systemic elevation of Th2 cytokines with increased IgE levels and eosinophilia in the acute phase[6,8]. However, Th1cytokines are detected in chronic AD, suggesting that Th1 cytokines are involved in the maintenance of chroic

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AD skin[8,9]. Additionally, a study has reported that number of Th17 cells is significantly increased in AD patients[10]. Thus these alternative concepts in AD should be addressed. Tacrolimus mainly acts on both Th1 and Th2 cells and then IFN-γ, IL-2, IL-4 and IL-5 are potently inhibited by tacrolimus[11]. Moreover, treatments with several monoclonal antibodies for AD are clinically applied or the clinical trials are underway[12-14]. In this review, the role of PPAR in AD and the possibility of its agonist for the treatment of AD are discussed.

2. Peroxisome proliferator-activated receptors

PPARs are fatty acid activated transcription factors that belong to the nuclear hormone receptor family. They are initially known as transcriptional regulators of lipid and glucose metabolism, although further evidence has also accumulated for their other functions. Three PPAR isotypes, PPAR-α, PPAR-β/δ and PPAR-γ, encoded by separate genes, have been identified in vertebrates. The expression of each isotype exhibits distinct tissue distribution reflecting their functions[15]. The highest expression of PPAR-α is found in liver, and preferentially expressed in metabolically active tissues including kidney, heart, skeletal muscle and brown fat[15-17]. PPAR-β/δ is expressed in a wide range of tissues such as brain, kidney, heart and skin[18,19]. PPAR-γ is expressed in heart, skeletal muscle, colon, intestines, kidney, pancreas and spleen. In human skin, all PPAR isotypes are expressed[4]. In skin, PPAR isotypes show the different expression pattern. PPAR-β/δ is ubiquitously present throughout the epidermis while the expression of PPAR-α and -γ increase along with the differentiation of keratinocytes[20]. Ligands of PPARs comprise long chain polyunsaturated fatty acid (**Table 1**). For example, α-linoleic acid, docosahexaenoic acid, arachidonic acid metabolites, and leukotrienes are the well-known endogenous ligands for PPARs. Many synthetic ligands for PPARs have been developed. Of them, fabric acid derivatives, dual-selective agonists for PPAR-α and -γ, and thiazolidinedione and derivatives, single-selective agonists for PPAR-γ, are successfully used in treatments of cardiovascular diseases and diabetes mellitus type 2[21,22]. However, any ligand for PPARs has not been clinically applied for the treatments of skin diseases. Previous studies have demonstrated underlying mechanisms in PPARs actions[23]. Once PPARs bind to their ligands, they form heterodimers with the retinoid X receptor (RXR), followed by direct binding to DNA response element, termed PPAR response elements (PPREs), located in the promotor regions of target genes[24-26]. Binding of ligand leads to the recruitment of coactivator complexes which modify chromatin structure and facilitate assembly of the general transcriptional machinery to the promoter[27]. This transactivation induces the expression of target genes, involved in PPARs functions (**Figure 1**).

	Single-selective				Dual-selective		
Ligand	PPAR-α	PPAR-β/δ	PPAR-γ	Ligand	PPAR-α	PPAR-β/δ	PPAR-γ
15-deoxy-D-12,14-PGJ_2			+	9-HODE	+		+
Leukotrien B_4	+			13-HODE	+		+
PGA_1		+		15-HETE	+		+
PGA_2		+		Linoleic acid		+	+
PGD_2		+		Palmitic acis	+	+	
PGI_2		+		Eicosapentanoic acid		+	+
8(S)-HETE	+			Clofibrate	+		+
Oleic acid	+			Fenofibrate	+		+
Oleoylethanolamide	+			WY14643	+		+
Thiazolidinediones			+	Ibuprofen	+		+
Fmoc-leucine			+	Indomethacin	+		+
Sulindac			+	Fenoprofen	+		+
GW0742		+		Farglitazar	+		+
GW1929			+	GW2331	+		+
GW2570			+	GW2433	+	+	
GW7845			+	GW409544	+		+
GW9578	+						
GW501516		+					

HETE: hydroxyeicosatetraenoic acid, HODE: hydroxyoctadecadienoic acid, PG: prostaglandis

Table 1. Endogenous and synthetic ligands of PPARs

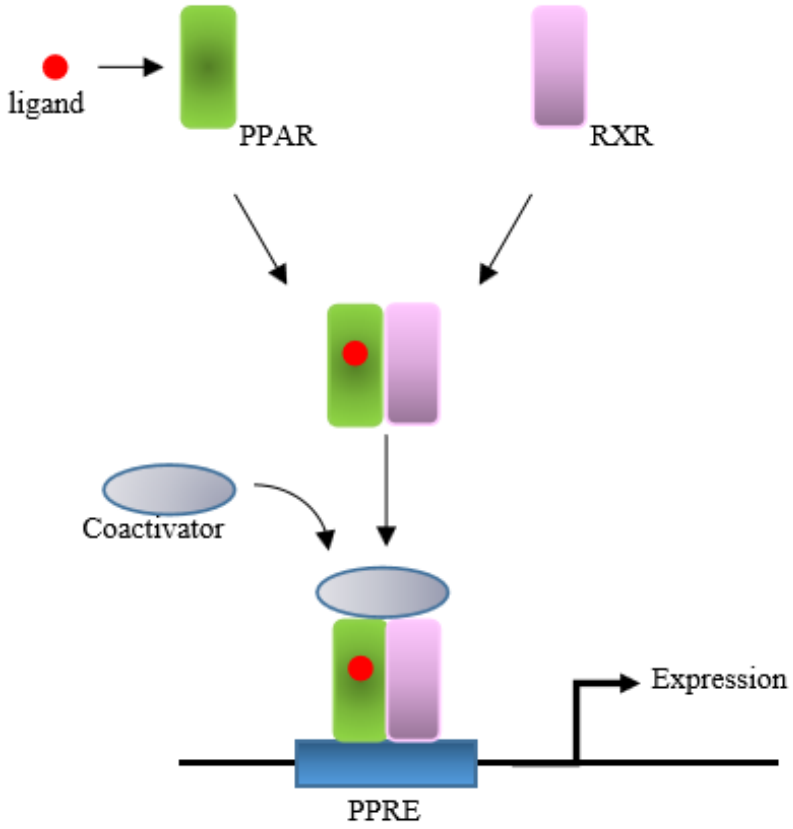

Figure 1; Mechanism of gene expression by PPAR activation. Specific ligands-activated PPARs form hetrodimers with retinoid X receptors (RXRs) and recruit cofactors. The complexes then modulate DNA transcription by binding to peroxisome proliferator response element (PPRE) in the promoter region of target genes.

3. Roles of PPARs in inflammation

Inflammation evoked by detrimental stimuli is a protective response in order to maintain homeostasis. Because innate immunity is considered as the first line of host defense against onset of harmful stimuli, immune cells such as macrophages, dendritic cells, mast cells, lymphocytes and neutrophils play crucial roles in complicated inflammation response. Apart from immune cells, non-immune cells such as keratinocytes, fibroblasts, epithelial cells and endothelial cells contribute the response as well[28,29]. In skin, once inflammatory stimuli are recognized by pattern-recognition receptors on the plasma membrane, inflammatory cytokines (e. g. TNF-α, IL-1β, IL-6) released from keratinocytes, fibroblasts and dendritic cells induce mediators during autocrine and paracrine signaling, followed by progression of the sophisticated inflammation process. Leukocyte adhesion, extravasation and migration to the inflammatory site are important events in leukocyte recruitment. Vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) play pivotal roles in leukocyte adhesion and their expression is the consequence of stimulation by TNF-α and IL-1, while they are not present on quiescent endothelial cells[30]. On the other hand, IL-8, which is induced by TNF-α, leads leukocyte, especially neutrophil, to migrate along a chemotactic gradient to the inflammatory site[31]. The initial demonstration of a regulatory function of PPAR-α in inflammation signaling was obtained in PPAR-α-deficient mice that display an exacerbated response to inflammatory stimuli[32]. Consequently, intensive studies on the effects of PPAR activators on inflammatory responses have been revealed that all of PPAR isotypes exert distinct and overlapping anti-inflammatory effects[33-40]. The effects of PPARs activation on inflammatory molecules are listed in **Table 2**[39,41]. Previous studies reported that a crosstalk between PPARs and transcription factors mediating inflammatory signaling including C/EBP, STAT, AP-1 and NF- B and proposed that five mechanisms of PPAR-mediated transrepression; i) direct interaction, ii) induction of IκBα, iii) regulation of kinase activity, iv) coactivator competition and v) co-repressor interaction[27,39,42]. The

reduction of IL-1-stimulated IL-6 production from human smooth muscle cells by fenofibrate is caused by the repression of c-Jun, a component of AP-1, and NF- B-induced transcription of the human IL-6 promotor. This transcription interference occurs independent to the promotor context. Furthermore, in vitro protein-protein interaction assay showed fibrate-activate PPAR-α binds directly to c-Jun and NF-κB (**Figure 2a**)[43]. Another study demonstrated a distinct mechanism that fenofibrate induces the expression of IκB, which inhibits NF-κB by masking the nuclear localization signals of NF-κB proteins and keeping them sequestered in an inactive state in the cytoplasm, in human aortic smooth muscle cells and hepatocytes, accompanied with a decrease in NF-κB DNA binding activity[44]. This suggests that PPAR activation inhibits NF-κB DNA binding by IκB induced by PPAR activation (**Figure 2b**). In mice colon inflammation, troglitazone reduces TNF-α and IL-1β mRNA levels, accompanied with reduction of NF-κB DNA binding activity, c-Jun NH2-terminal kinase (JNK), and p38 activities[45]. Oxidative stress-induced production of TNF-α and IL-1β is reduced in PPAR-γ overexpressing Ad/PPARγ C2C12 cells, compared to Ad/LacZ C2C12 cells. At the same time, phosphorylation of ERK1/2 and p38 is inhibited in Ad/PPARγ C2C12 cells, concomitant with inhibition of NF-κB translocation from cytosol to nucleus[46]. Likewise, Shi and the colleagues demonstrated that alline, a potent PPAR-γ activator, ameliorates LPS-induced production of iNOS, IL-1β, IL-6 and TNF-α from RAW264.7 cells through the reduced phosphorylation of ERK1/2, JNK and p38, suggesting that PPAR-γ activation regulates MAPKs activity[47]. These suggest PPAR activation attenuates inflammatory response through regulation of protein kinase activity (**Figure 2c**). Several members of the nuclear receptor family including PPARs and RXR require coactivator such as CREB-binding protein (CBP)/p300 to exert their functions. Similarly, AP-1 also requires CBP/p300 to regulate the target gene expression. Thus, PPARs and AP-1 scramble competitively for limiting pool of overlapping sets of coactivator in cells[48]. Li *et al*. have demonstrated that transrepression by PPAR-γ is achieved by targeting CBP through direct interaction with its N-terminal domain and via SRC-1-like bridge factors[49]. This is the fourth mechanism of transrepression (**Figure 2d**). Lee and the colleagues proposed a ligand-dependent transcriptional pathway in which PPAR-β/δ controls an inflammatory switch through its association and disassociation with BCL-6[50]. PPAR-β/δ-BCL-6 complex possesses pro-inflammatory effect when PPAR-β/δ is unliganded. Once PPAR-β/δ activated by the ligand, BCL-6 is released from the complex and then suppresses the production of cytokines and chemokines (**Figure 2e**). Pascual *et al* proposed another corepressor-dependent model that PPAR-γ mediates transrepression of a subset of inflammatory response genes in macrophages by preventing the signal-dependent clearance of corepressor complexes on inflammatory promoters downstream of LPS signaling[51]. Based on its anti-inflammatory activities as described above, PPARs are expected to be therapeutic targets for treatment of different inflammatory skin diseases[52].

Up-regulation	Down-regulation
IL-4, IL-5, sIL-1ra	IL-1β, IL-6, IL-12, IL-23, IL-27
	CCL2 (MCP-1), CCL4 (MIP), CXCL8 (IL-8)
	IFN-γ, TNF-α
	ICAM-1, VCAM-1
	ET-1
	COX-2, iNOS

Table 2. Influence of PPAR activation on inflammatory molecule expression

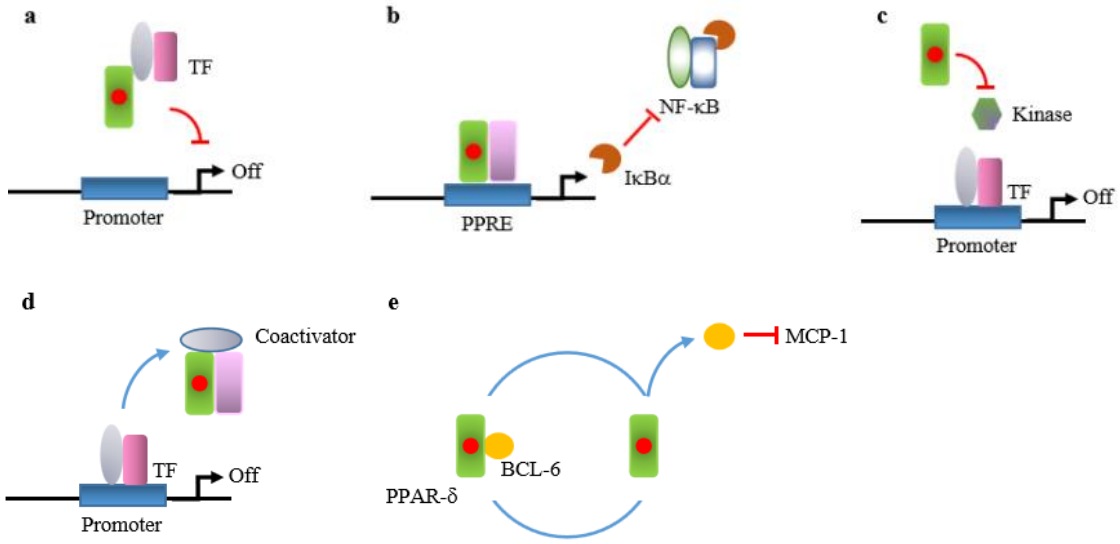

Figure 2; Mechanisms of liganded PPAR-mediated transsppression. a) Direct interaction with transcription factor (TF), b) Induction of IκBα, c) Kinase inhibition, d) Competitive scramble for coactivator, e) Association and disassociation with BCL-6**.**

4. Skin barrier disruption in atopic dermatitis

Atopic dermatitis (AD) is a chronic and relapsing disease. Its increasing prevalence to be estimated up to 20% in children and 10% in adults represents a major public-health problem. AD is characterized skin barrier dysfunction and immune dysregulation. From the aspect of skin barrier dysfunction, a typical characteristic of AD is xerosis which affects lesional and non-lesional skin areas, due to increased transepidermal water loss. Previous studies have proposed two major causes of increased transepidermal water loss: (i) decreased ceramide content in strarum corneum[53], (ii) filaggrin gene mutation[54]. This skin barrier disturbance exacerbates AD, due to facile penetration of molecules such as antigens[5]. Thus, the application of emollients such as urea and heparinoid is one of the basic treatments to support skin barrier function and allow hydration of the skin as conservative treatments[6]. On the other hand, it is supposed that hyperproliferation and hypodifferentiation of keratinocyte are the factors for skin barrier dysfunction in AD, other than gene mutation[55,56]. A previous report demonstrated that PPARβ/δ plays crucial roles in keratinocyte proliferation, maintenance of cutaneous barrier homeostasis and regulation of inflammation in PPARβ/δ deficient mice[57]. To establish a mature skin barrier function mechanically, sequential and orchestrated cross-linking of filaggrin, involucrin, loricrin and ceramides by transglutaminase 1 along with keratinocyte differentiation is required. Hanley *et al*. reported that clofibrate, a PPARα agonist, decelerates keratinocyte proliferation and accelerate differentiation with enhancement of mRNA expression of involucrin and transglutaminase 1[58]. Other studies demonstrated that caffeic acid induces keratinocyte differentiation via PPAR-α activation[59], and that GW0742, a PPAR-β/δ selective activator, induces keratinocyte differentiation and inhibits proliferation[60]. Addition to the regulation of keratinocyte differentiation, intracellular lipid accumulation and lamellar body secretion are crucial for the construction of intercellular lipid alignment to contribute skin barrier function. Schmuth *et al*. provided crucial evidence on relation between PPAR-β/δ activation and skin barrier homeostasis: i) PPAR-β/δ activator, GW1514, stimulates the recovery of acute and chronic skin perturbation in hairless mice, ii) GW1514 stimulates an increase in the expression of the differentiation markers, loricrin and filaggrin, iii) GW1514 increases accumulation of triglyceride[61]. A consecutive study from the same group demonstrated that application of activators of PPARα (WY14643), PPARβ/δ (GW1514) and PPARγ (ciglitazone) to hairless mice enhances synthesis of cholesterol, fatty acid and ceramides, and consequently that the activators accelerate the recovery from acute disruption of skin barrier function[62]. These results suggest that PPAR activators are expected to improve cutaneous barrier homeostasis by control of keratinocyte differentiation. Further, other studies showed that activation of PPAR-α by WY14643 improves skin barrier

with normalization of the molar ratio of the main skin barrier lipids to 1:1:1 (free fatty acids:ceramides:cholesterol) and upregulation of filaggrin expression[63], and that oat lipid extract, which demonstrates robust dual agonism for PPAR-α and PPAR-β/δ, enhances keratinocyte differentiation and ceramide synthesis[64]. These results suggest that PPAR activators are expected to be alternative treatments to support skin barrier function.

5. Attenuation of innate immunity in AD

On the other hand, immune dysregulation in both innate and acquired immunity is another important aspect in AD. Especially, cytokines in innate and acquired immunity contribute to establish the pathology of AD[65]. The innate immunity presents in epidermis as the front line defense against infection. Antimicrobial peptides (AMPs) such as cathelidin (LL37) and β-defensins, directly kill a broad spectrum of microbes, including Gram-positive and Gram-negative bacteria as well as fungi and certain viruses, are secreted from keratinocyte and activated to respond immediately after microbial invasion. Although it is supposed that AD patients have a higher prevalence of infection with bacteria, fungi, and viruses due to skin barrier disruption, the defects of innate immune system are demonstrated previously[7]. Ong *et al*. reported that the expression of LL37 and human β-defensin 2 (HBD-2) was suppressed in AD patients[8]. As the expression of AMPs arises during keratinocyte differentiation, the disturbance of keratinocyte differentiation is a considerable reason why suppression of LL37 and HBD-2 occurs in AD patients. Because PPARs activators induce keratinocyte differentiation[59,61,66,67], PPAR activation may improve AMPs production in AD. Furthermore, a previous study reported that apoptosis signal-regulating kinase-1 (ASK1), an intracellular regulator of keratinocyte differentiation, enhances the expression of LL37 and HBD2 via p38 cascade[68]. Since PPAR/p38 pathway is one of the signal cascade to exert the functions, similar to ASK1[69,70], PPAR activation is expected to induce AMP expression via p38. In fact, Dai *et al*. showed that PPARγ regulates the 1α, 25-dihydroxyvitamin D_3-induced production of HBD-3 and LL37, whose gene is a direct target of the vitamin D receptor, in keratinocytes through the regulation of AP-1 and p38 activity[71-74].

6. Dysregulation of acquired immunity in AD

Regarding dysregulation of acquired immunity, AD is originally considered as a Th2-mediated disease because of the systemic elevation of Th2 cytokines with increased IgE levels and eosinophilia in the acute phase[6,8]. Once keratinocytes, locating the outmost of the body, are activated by diverse stimuli including chemicals, allergens, microbes and scratching, they release thymic stromal lymphopoetin (TSLP), IL-25 and IL-33. TSLP is produced from keratinocytes by tape stripping-induced skin barrier disruption and by *Staphylococcus aureus*, as well as antigen-activated mast cells (MC)[75-77]. Additionally, the high expression of TSLP in keratinocytes from patients with AD implies involvement of TSLP in AD[78]. Previous studies demonstrated that IL-25 expression is found in Th2 cells, allergen-activated MCs, eosinophils, basophils, dendritic cells (DC) and human skin of AD patients[79-82]. IL-33 is expressed by a wide variety of cell types, including residing and infiltrating cells in skin[83]. These cytokines share the properties which induce IL-4, IL-5 and IL-13 production to lead skewing and augmenting Th2 response in AD[79,81]. Interestingly, a previous study demonstrated that TNF-α-induced HBD-2 production from HaCaT cells is significantly decreased in the presence of IL-4 or IL-13[7], suggesting that IL-4 and IL-13 affect the innate immune system in AD. In addition, IL-25 is suggested to participate in barrier dysfunction in AD because IL-25 reduces filaggrin expression in keratinocyte[81]. Additionally, IL-33 stimulates MCs to produce IL-5, IL-6, IL-10, IL-13, TNF-α and GM-CSF[84]. Of them, TNF-α stimulates keratinocytes to produce TSLP[65]. Following the production of TSLP, IL-25 and IL-33 to target Th2 cells, Th2-cytokines including IL-4, IL-5 and IL-13 are released. Their functions in acquire immune response are; i) IL-4 induces immunoglobulin class switch form IgM to IgE, and upregulates IgE receptors on monocytes, as well as promotion of Th2 skewing, ii) IL-5 induces the production of IL-25 from eosinophils and stimulates maturation and also activation of eosinophis, iii) the effects of IL-13 are similar to those of IL-4. The patients with AD are divided into extrinsic AD (EAD) and intrinsic AD (IAD). In EAD, increased total serum IgE and a higher

expression of IgE receptors on monocytes are found, compared with IAD. On the other hand, higher expression of IL-5 and IL-13 are detected in EAD than IAD. However, the expression of Th2 cytokines including IL-4, IL-5 and IL-13 in skin lesions of both group is elevated, compared with normal control skin[85-87]. IL-31, belonging to an IL-6 family in terms of its structure and receptor complex, is expressed by Th2 cells[88]. Raap *et al*. reported a correlation between serum levels of IL-31 and the severity of AD[89]. A role of IL-31 is to induce the release of pro-inflammatory cytokines including IL-1β and IL-6, and AD-related chemokines including CXCL1, CXCL8, CCL2 and CCL18 from eosinophils whose infiltration in skin lesions is a predominant pathological feature of AD[90]. In addition, IL-31 is focused as a major pruritogen associated with AD[91]. Because scratching behavior due to pruritus is an exacerbation factor to influence the quality of life, the control of pruritus is important. In NC/Nga mice developing spontaneously AD-like skin lesions, long-lasting scratching behavior and IL-31 expression is enhanced, while both of them is unchanged in TNCB-induced contact dermatitis and this scratching behavior is ameliorated by administration of anti-IL-31 antibody[92,93]. These suggest the importance of Th2 cytokines in the pathogenesis of acute phase in AD. It is well known that cytokine profile in AD shifts from Th2 dominant in acute phase to Th1 dominant in chronic phase, as it is called "Th1/Th2 paradigm"[94-97]. Indeed, increased levels of IL-12 and IFN-γ, which represent Th1 cytokines, are detected in chronic AD lesions, compared with normal skin[8]. Previously, Aral *et al*. demonstrated that serum level of IL-18 is found significantly higher in AD patients than in controls and that a statistically significant relationship between the severity of AD, and serum levels of IL-18 and IL-12/p40 is determined, suggesting the involvement of IL-18 in AD[9]. IL-18, derived from dendritic cells, induces Th1 cells to produce Th1 cytokines[66, 98]. Moreover, other studies suggest the roles of IL-18 in the pathogenesis of AD[99-101]. However, because the conflict results in relationship between IL-18 and atopic dermatitis-like inflammation[102], the role of IL-18 in atopic dermatitis should be further addressed. IL-21, a member of the type I cytokine family, is produced by lymphoid cells such as activated $CD4^+$ T cells and exerts its pleiotropic function by binding to IL-21 receptor (IL-21R). Upregulation of IL-21 and IL-21R in skin lesions from AD patients and elevated levels of IL-21 in serum form AD patients are reported[103, 104]. In mice, skin barrier disruption, a surrogate for scratching, enhances the expression of IL-21 and IL-21R, as well as IL-6[103]. Further, IL-21 enhances CCR7 expression, migration to local lymphnode and antigen presentation of DCs[105]. In addition to Th1/Th2 paradigm, Th17 cells and Th22 cells emerged as new participants in the pathogenesis of AD. The cell number of intracellular IL-17 positive circulating lymphocyte, mRNA expression of IL-17 in peripheral blood mononuclear cells and IL-17 concentration in serum are upregulated in the patient with AD, correlated with the severity of AD[106,107]. IL-17 directly enhances IgE production, but not IgG, IgM or IgA, in human by triggering rapid degradation of IκBa and subsequent translocation of NF-κB into the B-cell nucleus[108]. Th22 cells were identified as CD4+ T cell producing IL-22 and lacking production of IL-17 and are distinct from Th1, Th2 and Th17 cells[109-111]. IL-22 induces the expression of S100A7, S100A8 and S100A9, a group of proinflammatory molecules, in human keratinocyte, as well as matrix metalloproteinase 3 and CXCL5. In addition, IL-22 induces keratinocyte migration in an in vitro injury model and downregulates the expression of keratinocyte differentiation markers including involucrin, loricrin, heat shock protein 27, calmodulin-related protein and heme oxygenase 1. Further, in reconstituted human epidermis, IL-22 induces strongly hyperplasia[112]. The number of Th2 and Th22 cells are significantly elevated in AD, whereas psoriatic skin has significantly increased frequency of Th1 and Th17 cell. The levels of IL-22 is upregulated in AD lesions, associated with the severity of AD symptoms[113]. These findings suggested that IL-22 affects to maintenance of inflammation and epidermal hyperplasia in AD. Taken together, AD is a Th2/Th22 skewed disease, with additional contributions from Th1 cytokines occurring in the chronic stage. Overlooking this complicated pathogenesis of AD, a simple question, whether this complicated cytokine network in AD can be regulated by the activation of PPARs, is raised. To simplify the cytokine network, the intracellular signaling pathway activated by these cytokines are focused. As shown in **Table 3**, JAK/STAT or NF-κB is involved in all

signaling pathways activated by cytokines in AD. PPAR-α interacts with NF-κB and AP-1 and PPAR-γ interacts with STAT, NF-κB, AP-1 and NF-AT[42]. Consequently, the gene expression in the down-stream involving by these transcription factors is reduced. Likewise, we examined the effects of PPAR-δ activation by GW501516 on IL-6 and IL-8 production from HaCaT cells, an immortalized keratinocyte derived from human epidermis. Expectedly, LPS-induced IL-6 production and TNF-α-induced IL-8 production are reduced with GW501516 treatment (**Figure 3**). Following the results from in vitro experiments, in vivo experiments in animal models, including gene-modified animals and classical (traditional) animal, are required to elucidate the effect of PPAR activation on AD. Actually, Kim *et al*. demonstrated that ursolic acid, a potential PPAR-γ agonist, suppresses ovalbumin-induced airway inflammation with the downregulation of IL-5, IL-13 and IL-17[114]. In dermatological field, two groups reported the effect of PPAR activators on oxazolone-induced contact dermatitis in mice, as an atopic dermatitis model[115,116]. NC/Nga mouse is known as an animal model for AD. NC/Nga mice are originated from Japanese fancy mice (Nishiki-Nezumi) and were established as a inbred strain in 1955. The most important characteristic in NC/Nga mice is that spontaneous AD-like dermatitis appears in the mice raised under ambient laboratory conditions, while no skin lesion is detected clinically in the mice raised under specific pathogen-free condition. Additionally, previous studies have revealed the other features, including the skin barrier dysfunction with the reduction of ceramide contents, IgE hyperproduction, cytokine profiles and long-lasting scratching behavior, corresponding to human AD[117-120, 92]. Therefore NC/Nga mice are widely used for evaluation of the therapeutic effect for AD. Chiba *et al*. showed that topical application (transdermal) of PPAR-α suppresses atopic dermatitis in NC/Nga mice[121]. Recently, a study showed that tannic acid ameliorates clinical severity in house dust mite extract-induced AD-like dermatitis in NC/Nga mice, with pathologically inhibition of hyperkeratosis, parakeratosis, acanthosis and infiltration of inflammatory cell[122]. To follow the antecedent studies on the effect of PPAR activation on skin barrier dysfunction in AD, further studies should be performed to elucidate the effects of PPAR activation on immune-modulation in AD.

Cytokine	Kinase/Transcription factor
IL-4	JAK3/STAT6
IL-5	RAS/MAPK, JAK/STAT, PI3K
IL-13	JAK3/STAT6
IL-22	JAK1/STAT3, Tyk2/STAT3, MAPK/STAT3
IL-25	NF-κB
IL-31	JAK1/STAT3, JAK1/STAT5, JAK2/STAT3, JAK2/STAT5, PI3K/AKT
IL-33	NF-κB
TSLP	JAK2/STAT3, JAK2/STAT5

Table 3. Kinases/Tanscription factors in signaling pathways of AD cytokines

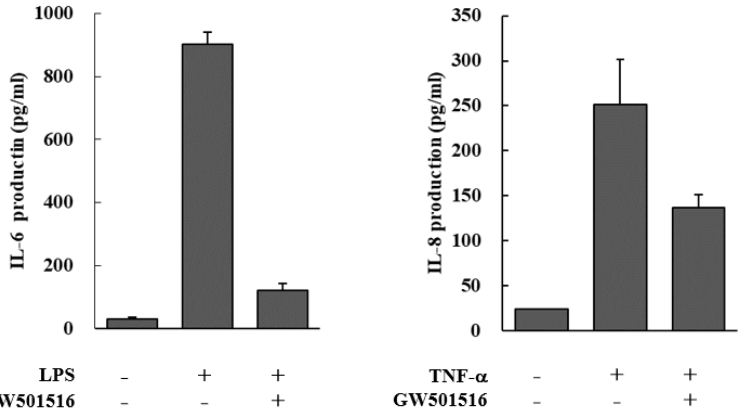

Figure 3; Suppression of inflammatory cytokine production by PPAR-δ agonist (GW501516). Treatment with GW501516 suppresses LPS-induced IL-6 production and TNF-α-induced IL-8 production from HaCaT cells**.**

7. Conclusion

Depending to pleiotropic function of PPARs, therapeutic applications of PPAR activators have been expected. Actually, some of agonists for PPAR-γ have already used in diabetes therapy. It is easily hypothesized that PPAR activators, which possess suppressive effects on transcription factors, may improve skin inflammation, including AD. Indeed, numerous numbers of in vitro experiments have been performed and provided useful information. Regarding to AD, although previous studies suggest that PPAR activation may be useful for improvement of skin barrier dysfunction and that PPAR activation suppresses the inflammatory molecules via inhibition of transcriptional pathways, the usefulness of PPAR activation for immune dysregulation is still unclear, due to its complicated cytokine network. However, some in vivo studies put the beacons to resolve the underlying issues. Thus, PPAR activation is expected to be one of the immune-modulating therapy for AD.

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