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Original article

Periostin contributes to epidermal hyperplasia in psoriasis common to atopic dermatitis

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ABSTRACT

Background: Epidermal hyperplasia is a histological hallmark observed in both atopic dermatitis (AD) and psoriasis, although the clinical features and the underlying immunological disorders of these diseases are different. We previously showed that periostin, a matricellular protein, plays a critical role in epidermal hyperplasia in AD, using a mouse model and a 3-dimensional organotypic coculture system. In this study, we explore the hypothesis that periostin is involved in epidermal hyperplasia in psoriasis.
Methods: To examine expression of periostin in psoriasis patients, we performed immunohistochemical analysis on skin biopsies from six such patients. To investigate periostin's role in the pathogenesis of psoriasis, we evaluated periostin-deficient mice in a psoriasis mouse model induced by topical treatment with imiquimod (IMQ).
Results: Periostin was substantially expressed in the dermis of all investigated psoriasis patients. Epidermal hyperplasia induced by IMQ treatment was impaired in periostin-deficient mice, along with decreased skin swelling. However, upon treatment with IMQ, periostin deficiency did not alter infiltration of inflammatory cells such as neutrophils; production of IL-17, −22, or −23; or induction/expansion of IL-17− and IL-22−producing group 3 innate lymphoid cells.
Conclusions: Periostin plays an important role during epidermal hyperplasia in IMQ-induced skin inflammation, independently of the IL-23−IL-17/IL-22 axis. Periostin appears to be a mediator for epidermal hyperplasia that is common to AD and psoriasis.

Introduction

Atopic dermatitis (AD) and psoriasis are the most common inflammatory skin diseases.[1] The clinical skin features of AD are highly pruritic eczematous erythematous plaques. In contrast, psoriasis is characterized by well-demarcated plaques with thick, nonadherent, silvery-white scales. Erythematous plaques and scales appear in both AD and psoriasis, but the features of the scales are different in these two diseases. In spite of the differing clinical features in AD and psoriasis, epidermal hyperplasia (acanthosis) is a histological similarity observed in these diseases.[1] It is assumed that epidermal hyperplasia provides a basis for supplying more massive proinflammatory mediators from keratinocytes. However, there is no satisfactory explanation of why epidermal hyperplasia is common in both diseases.

The underlying immunological disorders of AD and psoriasis are also significantly different. In AD, type 2 immune responses are dominant, particularly in the acute lesions, and type 1 responses are involved in the chronic stage.[2] In contrast, in the pathogenesis

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of psoriasis, TNF and IFN-α activates dendritic cells (DCs) followed by activation of type 1, type 17, and type 22 immune pathways.[3] For psoriasis, the IL-23–IL-17/IL-22 axis is critical for epidermal hyperplasia. Deficiency or blockage of IL-17, IL-22, or their receptors down-regulated epidermal hyperplasia in psoriasis model mice.[4–7] It has been assumed that keratinocyte proliferation factors such as IL-6 and tumor growth factor α, abundantly expressed in skin tissues of psoriasis patients, play pivotal roles in epidermal hyperplasia.[8] Accordingly, it has been postulated that epidermal hyperplasia by IL-23 is dependent on IL-6.[9]

Periostin, an extracellular matrix protein belonging to the fasciclin family, has been shown to be essential to the process of remodeling during tissue/organ development/repair and inflammation.[10,11] Periostin functions as a matricellular protein in cell activation by binding to receptors on the cell surface, thereby exerting its biological activities. We have shown that periostin plays a critical role in allergic skin inflammation induced by topical treatment with house dust mite extract (HDM) using periostin-deficient mice.[12,13] Deficiency of periostin caused impaired epidermal hyperplasia in addition to down-regulated skin inflammation. We furthermore revealed how periostin derived from fibroblasts causes proliferation and differentiation of keratinocytes using a 3-dimensional organotypic coculture system of keratinocytes and fibroblasts.[12,14] Periostin secreted from fibroblasts and IL-1α derived from keratinocytes synergistically act on fibroblasts to induce production of IL-6 by activating the NF-κB pathway. IL-6 secreted from fibroblasts acts on keratinocytes, inducing proliferation and differentiation. Thus, the epithelial–mesenchymal interaction involving periostin represents a mechanism capable of regulating proliferation and differentiation of keratinocytes in AD.

Given that epidermal hyperplasia is a common histological characteristic in AD and psoriasis and that periostin is critical for the induction of epidermal hyperplasia in AD, we hypothesized that periostin might be involved in epidermal hyperplasia in psoriasis as well. Our recent finding that serum periostin levels in psoriasis patients were lower than those of AD patients, but significantly higher than those of normal donors supports this idea.[15] In this study, we examined the expression of periostin in psoriasis patients and applied periostin-deficient mice to a psoriasis model using imiquimod (IMQ), an agonist of toll-like receptor (TLR) 7 and TLR8. We found substantial expression of periostin in all investigated psoriasis patients in a pattern similar to AD patients and that epidermal hyperplasia is decreased in IMQ-treated periostin-deficient mice. These results provide clear evidence that periostin is a mediator for the formation of epidermal hyperplasia common to both AD and psoriasis.

Methods

Human skin tissue specimens

Skin tissues examined for histology were obtained from four normal donors, five patients with psoriasis vulgaris, and one patient with psoriatic arthritis (Table 1). We primarily diagnosed psoriasis based on clinical manifestations and histopathological findings.[16] The six psoriasis patients examined for histology were from ages 40 to 77, three males and three females. No patients had comorbidities known to up-regulate periostin expression. A normal facial skin section was obtained from a non-psoriatic patient. All patient samples were taken after a medication-free period of at least two weeks.

Mice

Periostin-deficient (*Postn*$^{-/-}$) mice prepared as previously described (129SvJ; C57BL/6 background, Ref. 17) were backcrossed to BALB/c mice (Japan SLC, Shizuoka, Japan), and N7–N8 mice were used. Twelve-week-old *Postn*$^{-/-}$ mice and their wild-type or *Postn*$^{+/-}$ littermates as control were compared.

Table 1
Psoriasis patient information.

Patient	Age	Sex	Disease duration (mo.)	Biopsy	Clinical signs	Diagnosis
1	40	M	2	Mandible	Scales, erythema	Psoriatic arthritis
2	71	M	4	Palm	Scattered plaques	Psoriasis vulgaris
3	56	F	5	Lower leg	Multiple eruptions	Psoriasis vulgaris
4	58	F	6	Knee	Multiple eruptions	Psoriasis vulgaris
5	62	M	120	Lower leg	Multiple plaques, erythema, scale	Psoriasis vulgaris
6	77	F	180	Forearm	Erythema	Psoriasis vulgaris

Model mice of psoriasis

Model mice of psoriasis using IMQ were generated as previously described, with minor modifications.[4] A daily dose of 30 mg of 5% IMQ cream (Beselna cream; Mochida Pharmaceutical Co. Ltd., Tokyo, Japan) or control cream (hydrophilic petrolatum or Vaseline, Nikko Pharmaceutical Co. Ltd., Gifu, Japan) was applied to each ear for seven days. In Fig. 3G, IMQ was applied only to the right ear. The ear thickness was measured every day using calipers (Ozaki MFG, Tokyo, Japan). The difference in ear thickness between day 0 and every subsequent day was expressed as ear swelling.

Histology

Exiced ear lobes were fixed in 10% buffered formalin and embedded in paraffin. Deparaffinized sections were stained using hematoxylin and eosin (H&E). Epidermal thickness was measured at 10 random points per sample and expressed as an average value. Immunohistochemical staining for myeloperoxidase (MPO, polyclonal rabbit anti-human myeloperoxidase, Dako, Glostrup, Denmark) and periostin (rabbit anti-periostin IgG) was performed as described previously.[18]

Real-time quantitative PCR

Total mRNA was extracted from a half-cut ear, isolated using RNAiso Plus (Takara Bio, Otsu, Japan), and reverse-transcribed with the ReverTra Ace (Toyobo, Osaka, Japan). Quantitative PCR analyses were performed on a StepOnePlus real-time PCR System (Life Technologies, Carlsbad, CA, USA) using the Thunderbird SYBR qPCR mix (Toyobo). PCR primers were IL-1α (*Il1a*), forward primer, 5′-TTGGTTAAATGACCTGCAACA-3′, and reverse primer, 5′-GAGCGCTCACGAACAGTTG-3′; IL-6 (*Il6*), forward primer, 5′-GCTACCAAACTGGATATAATCAGGA-3′ and reverse primer, 5′-CCAGGTAGCTATGGTACTCCAGAA-3′; IL-17A (*Il17a*), forward primer, 5′-TGTGAAGGTCAACCTCAAAGTCT-3′, and reverse primer, 5′-GAGGGATATCTATCAGGGTCTTCAT-3′; IL-17F (*Il17f*), forward primer, 5′-CCCAGGAAGACATACTTAGAAGAAA-3′ and reverse primer, 5′-GCAAGTCCCAACATCAACAG-3′; IL-22 (*Il22*), forward primer, 5′-GCTCAGCTCCTGTCACATCA-3′, and reverse primer, 5′-AATCGCCTTGATCTCTCCAC-3′; IL-23p19 (*Il23a*), forward primer, 5′-TCCCTACTAGGACTCAGCCAAC-3′ and reverse primer, 5′-AGAACTCAGGCTGGGCATC-3′; IL-36α (*Il36a*), forward primer, 5′-TGCCCACTCATTCTGACCCA-3′, and reverse primer, 5′-GTGCCACAGAGCAATGTGTC-3’; IL-36β (*Il36b*), forward primer,

5′-CTTCGATCCCAGAGACAAGACT-3′ and reverse primer, 5′-ATTC GGTTCCCACATTTGAA-3′; CXCL2/MIP-2α (*Cxcl2*), forward primer, 5′-CCTGGTTCAGAAAATCATCCA-3′, and reverse primer, 5′-CTTCC GTTGAGGGACAGC-3′; S100A9 (S100a9), forward primer, 5′-CACCCTGAGCAAGAAGGAAT-3′ and reverse primer, 5′-TGTCATT-TATGAGGGCTTCATTT-3′; and GAPDH (*Gapdh*), forward primer, 5′-TCACCACCATGGAGAAGGC-3′, and reverse primer, 5′-GCTAAG-CAGTTGGTGGTGCA-3′. Threshold cycles of primer probes were normalized to a housekeeping gene, *Gapdh*.

Flow cytometry

Submandibular lymph nodes were consistently swollen at day 7 among mice with ears treated with IMQ. Lymph node samples were minced through a 40-μm nylon mesh (Cell Strainer, BD Biosciences, Franklin Lakes, NJ, USA) to obtain single-cell suspensions. Cells were rested in RPMI supplemented with 10% fetal calf serum overnight, and 2×10^6 cells/200 μl were stimulated with 50 ng/ml phorbol 12-myristate 13-acetate and 2 μg/ml ionomycin (Sigma-Aldrich, St. Louis, MO, USA) together with monensin (BioLegend, San Diego, CA, USA) for 6 h. Cells were stained with anti-CD3ε followed by intracellular staining using monoclonal antibodies (mAbs) PE-conjugated anti–IL-17A or anti–IL-22 (eBioscience, San Diego, CA, USA) after fixation and permeabilization with FIX & PERM reagent (Life Technologies). Samples were acquired on a FACSCalibur (BD Biosciences) and analyzed using FlowJo software (TreeStar Inc., Ashland, OR, USA).

Enzyme-linked immunosorbent assay (ELISA)

Mouse embryonic fibroblasts were cultured in DMEM supplemented with 10% FCS at 1×10^5 cells/ml overnight. The medium was then replaced with Opti-MEM I (Life Technologies) and stimulated with mouse recombinant IL-17 (Sigma-Aldrich), IL-21, IL-22, IL-36β (R&D Systems, Minneapolis, MN, USA), or IL-13 (PeproTech, Rocky Hill, NJ, USA) at 50 ng/ml for 24 h. The ELISA analysis for periostin in the supernatants was performed as described previously.[14]

Statistical analyses

Data are presented as mean ± standard deviations and analyzed by Student's *t*-test or repeated measures two-way analysis of variance (ANOVA), followed by Bonferroni's post-hoc tests. Data were analyzed using Prism (GraphPad, La Jolla, CA, USA) with the significance level α at 0.05.

Experiment approval

Animal experiments were undertaken following the guidelines for care and use of experimental animals of the Japanese Association

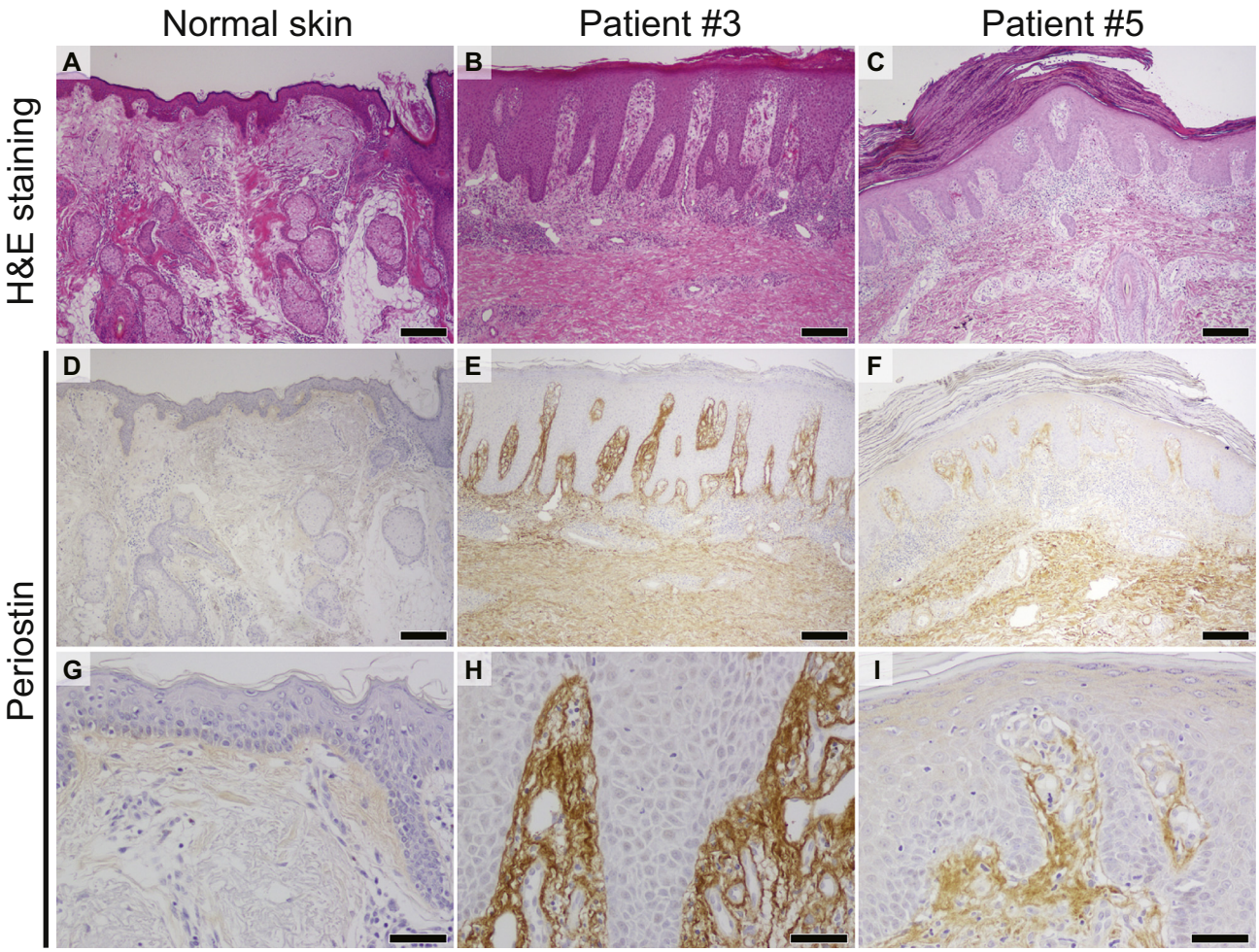

Fig. 1. Histological views of skin tissues of psoriasis patients. Histological sections stained with H&E (A–C) or immunostained against periostin (D–I) of a healthy subject (A, D, G) or psoriasis vulgaris patients (Patient #3; B, E, H, and Patient #5; C, F, I). Bars represent 200 μm (A–F) or 50 μm (G–I). Patients 3 and 5 are representatives with short and long disease duration, respectively.

for Laboratory Animals Science (1987) and the protocols approved by the Institutional Animal Care and Use Committee of Saga Medical School. Human studies were performed under protocols approved by the Ethics Committees of Juntendo University.

Results

Expression of periostin in psoriatic skin tissues

Expression of periostin protein was analyzed by immunohistochemistry on skin tissues derived from five patients with psoriasis vulgaris and one patient with psoriatic arthritis. The clinical features of these patients are listed in Table 1. All investigated samples showed enhanced expression of periostin compared with normal donors (Fig. 1). Periostin was exclusively expressed in the dermis of the patients, particularly at the epidermal border, similar to what has been observed in AD patients.[12] These results demonstrate that periostin is deposited in skin tissues of psoriasis patients in a pattern similar to that of AD, supporting our hypothesis that periostin may play some role in the pathogenesis of psoriasis, as it is known to AD.

Involvement of periostin in skin swelling in IMQ-treated mice

To investigate the role of periostin in the pathogenesis of psoriasis, we employed topical application of IMQ, a well-known mouse model of psoriasis.[4] Upon IMQ treatment, the ears of the mice started to swell the first day after initiation, and the swelling continuously increased until day 7 (Fig. 2A). The ears treated with IMQ showed erythema, scales, and hair loss (Fig. 2B). When we applied IMQ treatment to periostin-deficient littermates, ear swelling was significantly decreased (Fig. 2A, repeated measures two-way analysis of variance with Bonferroni's post-hoc test, $p < 0.0001$). The macroscopic features — such as erythema, scales, and hair loss — were milder in periostin-deficient mice than in control mice (Fig. 2B). There were no obvious sex-related differences in these features nor in ear swelling (Fig. 2B and data not shown). These results suggest that periostin is required during IMQ-induced skin inflammation in mice.

Involvement of periostin in epidermal hyperplasia in IMQ-treated mice

We then histologically analyzed skin tissues from IMQ-treated mice. The epidermis in the IMQ-treated control mice showed hyperplasia (acanthosis), hyperkeratosis, and parakeratosis characterized by retention of nuclei in the cornified layer, similar to psoriasis patients (Fig. 3A, B and D). Massive infiltration of neutrophils was observed in the dermis and were present in the epidermis like Munro's microabscesses in psoriasis patients (Fig. 3E and F). Lymphocytes and macrophages also significantly infiltrated the dermis. Topical treatment with IMQ transiently enhanced periostin expression extensively in the dermis at day 3, as observed in the psoriasis patients (Fig. 3G, day (d) 3, right), whereas periostin was only slightly expressed at the borders of the epidermis and dermis in non-treated mice or non-treated ears (Fig. 3G, d0 and 3, left). Epidermal thickness upon treatment with IMQ in periostin-deficient mice was significantly decreased (71.2%, $p < 0.0001$, Fig. 3C and D). Infiltration of neutrophils (MPO^+ cells) in the epidermis showed a tendency to decrease, but the difference was not statistically significant (Fig. 3F and data not shown). The observed infiltration of neutrophils and macrophages in the dermis was similar to that found in the control mice. These results suggest that periostin plays an important role in the process of epidermal thickness but not in the infiltration of inflammatory cells in the IMQ-treated mice.

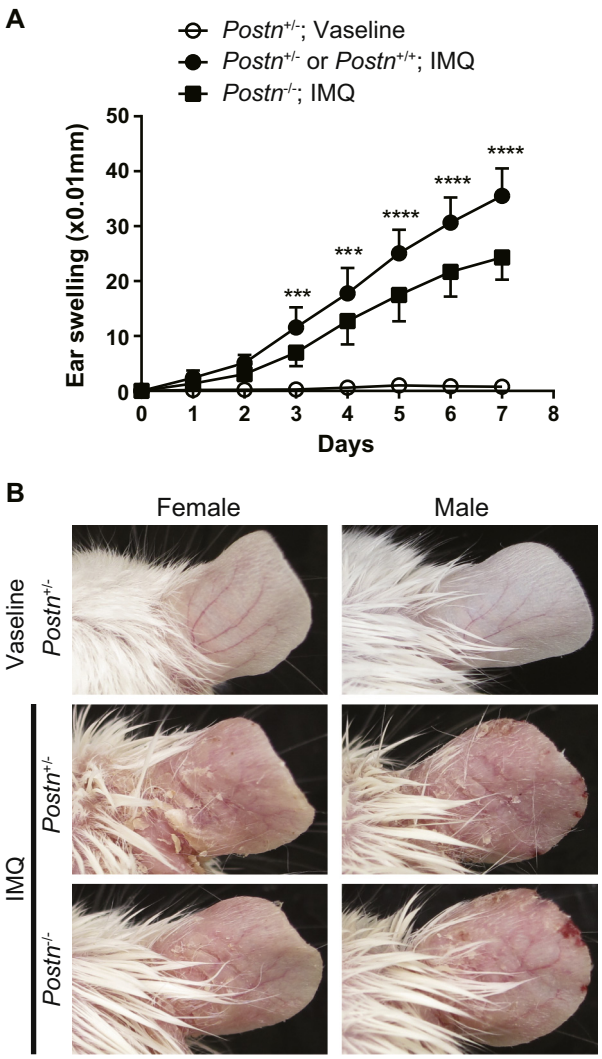

Fig. 2. Macroscopic changes of IMQ-treated mice. (A) Ear swelling of Vaseline-treated $Postn^{+/-}$ mice ($n = 4$), IMQ-treated $Postn^{+/+}$ or $Postn^{+/-}$ mice ($n = 24$), and IMQ-treated $Postn^{-/-}$ mice ($n = 15$) were depicted. Ear thickness before treatment was subtracted from the individual ear thickness. Data are presented as mean ± s.d. ***: $p < 0.001$, ****: $p < 0.0001$. (B) Representative posterior views of ears of Vaseline-treated $Postn^{+/-}$ mice and IMQ-treated $Postn^{+/-}$ and $Postn^{-/-}$ mice for both genders.

Periostin is not required for IMQ-induced production of proinflammatory cytokines/chemokines

It is known that type 1, type 17, and type 22 immune responses are triggered by TNF and IFN-α in the pathogenesis of psoriasis.[3] In particular, analyses of the model mice using IMQ show the critical role of the IL-23–IL-17/IL-22 axis in skin inflammation.[4–7] Moreover, it has been demonstrated that IL-36, a member of the IL-1 family, is involved in the pathogenesis of psoriasis by interacting with DC-keratinocyte cross-talk.[19] We then examined the role of periostin in producing IMQ-induced proinflammatory mediators. IMQ treatment increased expression of all investigated proinflammatory cytokines and chemokines, including *Il1a*, *Il6*, *Il17a*, *Il17f*, *Il22*, *Il23a*, *Il36a*, *Il36b*, and *Cxcl2* as well as *S100a9*, a neutrophil marker (Fig. 4). Expression of all of these proinflammatory cytokines and chemokines at mRNA level was not significantly altered in periostin-deficient mice. These results demonstrate that periostin is mostly dispensable for IMQ-induced production of proinflammatory cytokines/chemokines at mRNA level. However, we

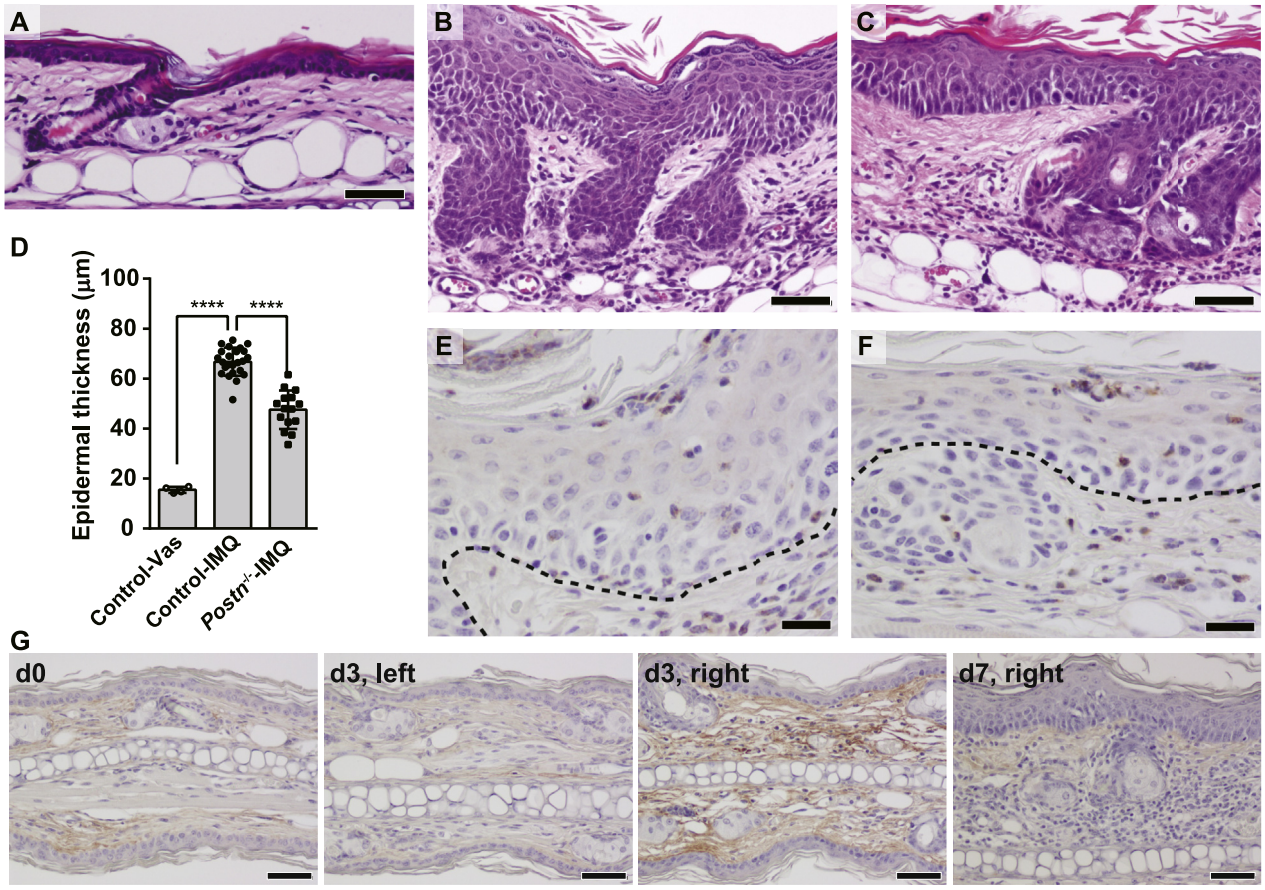

Fig. 3. Histological changes of IMQ-treated mice. Histological sections stained with H&E (A–C) or immunostained for MPO (E, F) of Vaseline-treated (A) or IMQ-treated (B, C, E, F) *Postn*$^{+/-}$ (A, B, E), or *Postn*$^{-/-}$ (C, F) mice. (D) Histological epidermal thickness of mice used in Fig. 2A. (G) Histological sections immunostained for periostin of IMQ-treated (right ear only) wild-type mice at days (d) 0, 3, and 7. Left ears were left untreated in this experiment. Bars represent 50 μm (A–C, G) and 20 μm (E, F). ****: $p < 0.0001$.

noted a consistent decrease, albeit not statistically significant, in mRNA expression of *Il17f* and *Il22* in independent sets of experiments (Fig. 4 and data not shown).

Periostin is dispensable for IMQ-induced activation/expansion of group 3 innate lymphoid cells (ILC3)

Recently, the significance of innate cells, such as γδ T cells and ILC3, has emerged as IL-17A– and IL-22–producing cells in various inflammatory diseases/states.[5,7] We next investigated the involvement of periostin in induction/expansion of IL-17A– and IL-22–producing γδ T cells and ILC3 by IMQ. We stained either IL-17A or IL-22 on expanded cells within the draining lymph nodes. Both IL-17A– and IL-22–producing cells in the CD3$^-$ fraction that contains ILC3 significantly increased, whereas those of the CD3$^+$ fraction that contains αβ and γδ T cells only slightly increased in the IMQ-treated mice (Fig. 5). The proportions of IL-17A– and IL-22–producing cells in the CD3$^-$ fraction were not significantly changed in periostin-deficient mice. These results suggest that periostin does not affect induction/expansion of IL-17A– or IL-22–producing ILC3 by IMQ, at least in the peripheral lymphoid tissues.

Failure to induce periostin expression by psoriasis-associated proinflammatory mediators

We have shown that IL-4 and/or IL-13, signature type 2 cytokines, induce expression of periostin in allergic inflammation/diseases.[12,18,20] In addition to IL-4 and IL-13,various factors—TGF-β 1, 2, and 3, bone morphogenetic proteins (BMP) 2 and 4, vascular endothelial growth factor, connective tissue growth factor 2, vitamin K, valsartan (an angiotensin II antagonist), and IL-3 and -6—are known to trigger periostin expression.[10] We examined the possibility that any of the psoriasis-associated cytokines would induce periostin expression, resulting in periostin being deposited in the skin tissues of psoriasis patients. However, none of the factors tested—IL-17, -21, -22, and −36β—induced expression of periostin in fibroblasts (Fig. 6). These results suggest the possibility that some factor(s) expressed in psoriasis patients other than IL-17, -21, -22, and −36β or the combination of multiple factors may induce periostin expression.

Discussion

In this study, we investigated both the expression and functional requirement of periostin in the pathogenesis of psoriasis. By using immunohistochemical analysis, we demonstrated that periostin is highly deposited in the dermis of psoriasis patients (Fig. 1). Accordingly, we recently found that serum periostin levels in psoriasis patients were significantly higher than those in normal donors.[15] We confirmed by immunohistochemistry that IMQ treatment induced at least a transient deposit of periostin in the dermis as observed in psoriasis patients (Figs. 1 and 3G). From these findings, we assume that the use of periostin-deficient mice in the IMQ-induced psoriasis-like dermatitis model corresponds to a study to investigate the effects of both basal and IMQ-induced periostin in this mouse model.

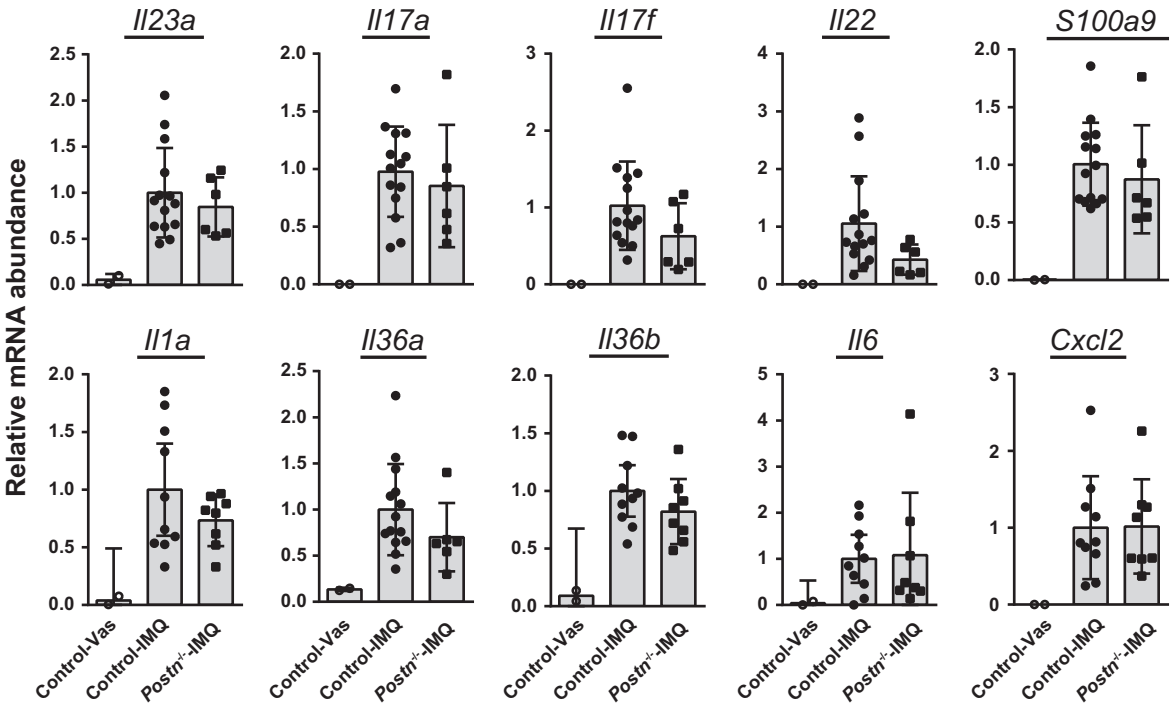

Fig. 4. Periostin expression does not affect IMQ-induced skin inflammation in mice. End-point (d7) quantitative RT-PCR analyses of various psoriasis-associated genes in mouse ears are shown in Fig. 2A. None of these genes showed a statistical significant difference between IMQ-treated control and *Postn*$^{-/-}$ mice.

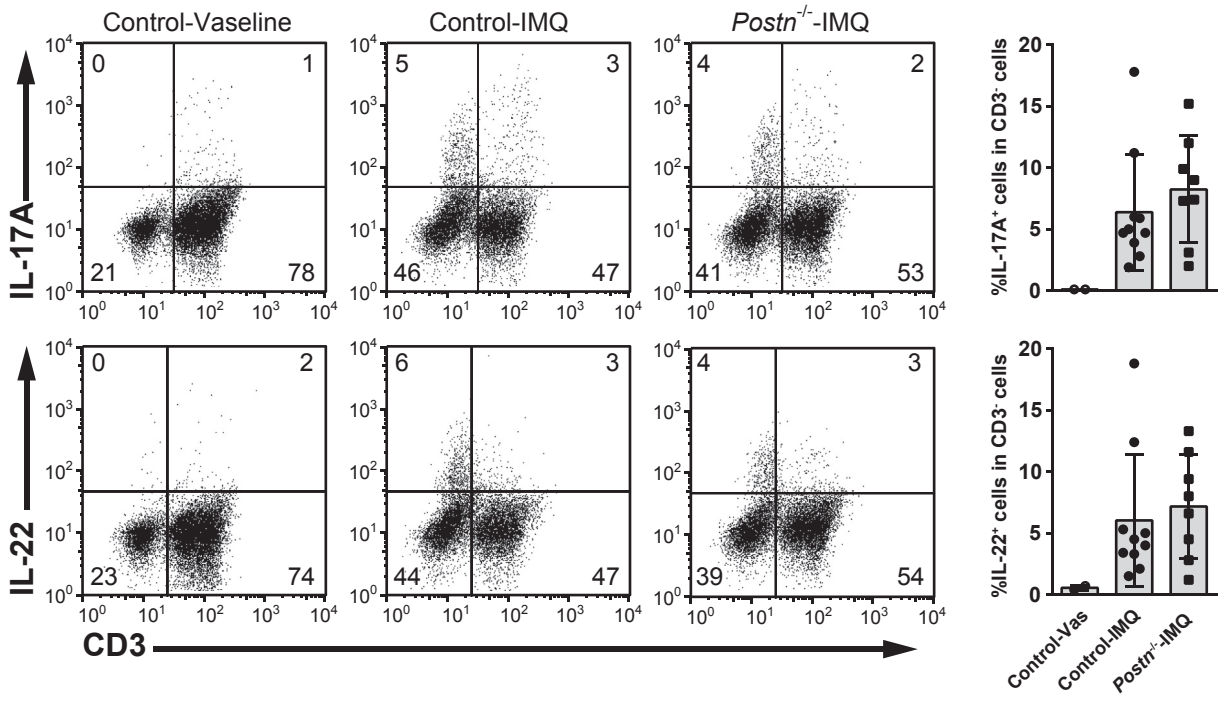

Fig. 5. Activation/expansion of ILC3 in IMQ-treated mice. Flow cytometric analysis of surface CD3 and intracellular IL-17A/IL-22 expression within cervical lymph node cells from Vaseline-treated control (*Postn*$^{+/-}$) and IMQ-treated control (*Postn*$^{+/-}$) and *Postn*$^{-/-}$ mice. The graphs show the percentages of IL-17A^{+} or IL-22^{+} cells in CD3^{-} cells.

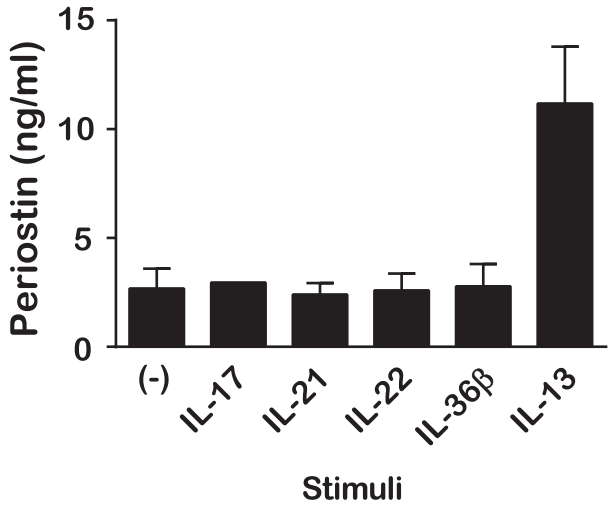

Fig. 6. Failure of induction of periostin expression by psoriasis-associated cytokines. Mouse embryonic fibroblasts were stimulated with 50 ng/ml indicated cytokines or left unstimulated (−) for 24 h. Amount of periostin in the supernatants was measured using ELISA.

We found by the analyses using periostin-deficient mice that periostin is important for epidermal hyperplasia, a common feature of both psoriasis and AD. This result raised the possibility that periostin would be a common mediator for epidermal hyperplasia in psoriasis and AD. Multiple lines of evidence have accumulated suggesting that periostin acts as a matricellular protein inducing cell proliferation such as keratinocytes in wound repair and malignant cells via the signal transduction pathways including FAK, PI3-kinase, Akt, ERK, NF-κB, and STAT3.[10,11] It is reasonable to assume that periostin expressed in skin tissues of psoriasis patients acts on keratinocytes as a matricellular protein inducing keratinocyte proliferation. We previously demonstrated that administration of the antibodies against α_V integrin down-regulated keratinocyte proliferation in the AD model mice and in the 3-dimentional organotypic coculture system.[12] We furthermore showed that induction of IL-6 expression in fibroblasts is one of the mechanisms by which periostin promotes keratinocyte proliferation.[14] Collectively, it can be assumed that IL-6 production by the interaction between periostin and α_V integrin on fibroblasts could be one of the mechanisms underlying epidermal hyperplasia in pathological status. However, IL-6 expression in the skin was invariant in IMQ-treated control and periostin-deficient mice (Fig. 4). This may be due to spatiotemporal mismatches between the *in vivo* IL-6 actions on keratinocytes and our analyses, which were performed only at the specified times and used the whole skin tissues. Alternatively, some effects of periostin on keratinocytes other than inducing IL-6 production may be important for keratinocyte proliferation in the IMQ-treated mice.

In contrast to epidermal thickness, infiltration of inflammatory cells such as neutrophils, production of IL-17, -22, and -23, and induction/expansion of IL-17− and IL-22−producing ILC3 induced by IMQ were not altered in periostin-deficient mice (Figs. 4 and 5). These inflammatory changes are likely due to the more immediate effects of IMQ, and the contribution of periostin is very limited or negligible. This result contrasts with our previous finding that type 2 immune responses are impaired in HDM-treated periostin-deficient mice.[12] These contrasting results clearly indicate that the involvement of periostin in the pathogenesis of AD and psoriasis differs in that acceleration of inflammatory responses by periostin observed in AD model mice is not involved in psoriasis model mice. Moreover, the present results suggest that the mechanisms of epidermal hyperplasia and inflammatory responses are uncoupled in the IMQ-treated mice. It has been proposed that the IL-23−IL-17/IL-22 axis is critical for epidermal hyperplasia in psoriasis.[4–7] However, our results demonstrate the presence of an IL-23−IL-17/IL-22 axis−independent pathway for epidermal hyperplasia in psoriasis.

We examined which psoriasis-associated cytokine—IL-17, -21, -22, and −36β—might induce periostin expression in fibroblasts, but none of these factors exerted such effect (Fig. 6). Some other factors expressed in psoriasis patients, or a combination of any of these factors, may induce periostin expression. Thus far, various factors—TGF-β1, 2, and 3, BMP2 and 4, vascular endothelial growth factor, connective tissue growth factor 2, vitamin K, valsartan, and IL-3 -4, -6, and −13—are known to induce periostin expression.[10] On the other hand, we and others have demonstrated that periostin is expressed in various inflammatory diseases/states such as AD,[12,15] IgG4-related sclerosing sialadenitis,[21] eosinophilic otitis media,[22] allergic rhinitis and chronic rhinosinusitis,[23] idiopathic or drug-induced pulmonary fibrosis,[24,25] scleroderma,[26] and proliferative diabetic retinopathy.[27,28] It has been largely undetermined what triggers periostin expression on each of these pathological states. Moreover, the molecular mechanism of periostin expression induced by various factors has remained unclear. Further studies aiming at clarifying these points are needed.

In conclusion, we demonstrate that periostin is highly expressed in the dermis of psoriasis patients, as it is in AD patients, and that periostin plays an important role in IMQ-induced epidermal hyperplasia in mice. These results provide us with strong evidence that periostin is a mediator for epidermal hyperplasia common to both AD and psoriasis.

Acknowledgments

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Conflict of interest

The authors have no conflicts of interest to declare.

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