

REVIEW ARTICLE

Periostin: An emerging biomarker for allergic diseases

Kenji Izuhara¹  | Satoshi Nunomura¹  | Yasuhiro Nanri¹ | Junya Ono^{1,2} | Masayuki Takai^{1,2} | Atsushi Kawaguchi³

¹Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan

²Shino-Test Corporation, Sagami, Japan

³Education and Research Center for Community Medicine, Saga Medical School, Saga, Japan

Correspondence

Kenji Izuhara, Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, 5-1-1 Nabeshima, Saga 849-8501, Japan.
Email: kizuhara@cc.saga-u.ac.jp

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Abstract

Periostin is a matricellular protein as well as an extracellular matrix (ECM) protein belonging to the fasciclin family. Periostin plays important roles as a matricellular protein in the setting of allergic diseases by binding to several integrins on various cells. Since periostin is induced mainly by IL-4 and IL-13, signature type 2 cytokines, and it is highly expressed in the subepithelial regions of many chronic allergic diseases, periostin has emerged as a novel biomarker reflecting type 2 inflammation in allergic diseases. It has, moreover, been revealed that periostin has characteristics different from other type 2 biomarkers such as eosinophil count and fractional exhaled nitric oxide (FeNO), reflecting fibrosis or tissue remodeling. From this, we may say that serum periostin is a “chronic” type 2 biomarker, whereas FeNO and possibly the eosinophil count are “acute” type 2 biomarkers. In contrast, it is still uncertain how we can apply periostin measurement to the use of biologics for allergic diseases. By examining the roles of periostin in allergy and the utility and potential of periostin in developing diagnostics against allergic diseases, it is hoped that in the near future, we can develop a new strategy to treat allergic patients.

KEYWORDS

biomarker, inflammation, matricellular protein, periostin, type 2

1 | INTRODUCTION

In 2006, the association of periostin with allergic diseases was reported for the first time.¹ Moreover, less than a decade has passed since it was reported in 2011 that serum periostin can predict the efficacy of lebrikizumab, a neutralizing anti-IL-13 antibody, in a phase 2 trial for asthma patients, showing for the first time the usefulness of periostin as a biomarker for allergic diseases.² Subsequently, our understanding of the pathological significance of periostin in allergic diseases has developed significantly, and tremendous attention has been paid to periostin as a novel biomarker for allergic diseases. As a consequence, it has been established that periostin is indeed a biomarker reflecting type 2 inflammation in allergic diseases. Moreover, it has been revealed that periostin has characteristics different from other type 2 biomarkers, such as eosinophil count and fractional exhaled nitric oxide (FeNO). However, it is still uncertain how we

can apply the measurement of periostin to the use of biologics for allergic diseases, in spite of the initial success with the development of lebrikizumab. Clearly, establishing how we apply biomarkers to use biologics is both critical and urgent if we are to achieve precision medicine in allergic diseases. In this review article, we explain the characteristics of periostin as a mediator and a biomarker for allergic diseases, and we review the status of periostin as a biomarker for determining treatments for them.

2 | FUNCTION OF PERIOSTIN IN STEADY STATE

Periostin is characterized as a matricellular protein as well as an extracellular matrix (ECM) protein belonging to the fasciclin family.³ Matricellular proteins are defined as ECM proteins that bind to

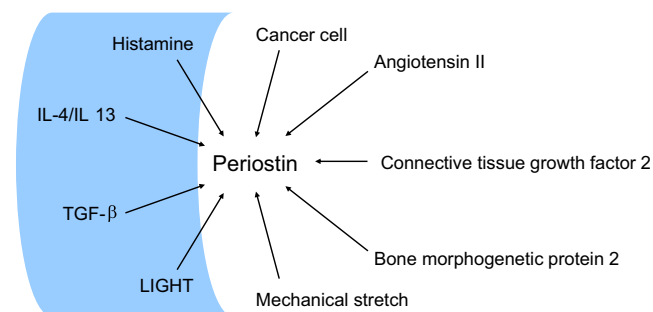


FIGURE 1 Periostin-inducing factors. The factors known to induce periostin are depicted. The factors correlated with allergic diseases are boxed in light blue

cell-surface receptors such as growth factors or cytokines and transduce cell signals.⁴ Periostin binds to several integrins— $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_6\beta_4$, and $\alpha_M\beta_2$ —transducing the signals via these receptors.³ Periostin also plays important roles as a matricellular protein in the development and repair of tissues or organs such as bones, skins, heart, and lungs. Periostin-deficient mice show growth retardation and dwarfism, shorter long bones, and decreased bone strength, suggesting that periostin mediates bone development/remodeling and bone strength by regulating collagen cross-linking and fibrillogenesis.^{5,6} Moreover, periostin is re-expressed during fracture repair or in response to mechanical stress, enhancing bone development and remodeling.⁷ In normal skin, periostin is predominantly expressed in the basement membrane and around hair follicles in the dermis.⁸ During excisional wound healing, expression of periostin is upregulated and is involved in the process of wound repair by enhancing myofibroblast-mediated wound contraction, re-epithelialization of the dermis, and dermal fibroblast activation.^{9–11} Periostin plays a central role in in utero and neonatal development of the cardiac valves and fibrous heart skeleton by promoting cardiac mesenchymal stem cell differentiation into fibrogenic lineages, collagen production, compaction, and fibroblast proliferation.¹² In contrast, during the remodeling following cardiac injury or hypertension, periostin is highly expressed and is involved in cardiac repair.¹³ Periostin plays a role in neonatal lung remodeling as well, because prolonged hyperoxic lung injury upregulates expression of periostin, which in turn stimulates ectopic accumulation of myofibroblasts, followed by alveolar simplification.¹⁴

3 | CHARACTERIZATION OF PERIOSTIN AS A MEDIATOR FOR ALLERGIC DISEASES

3.1 | Expression of periostin in inflamed sites of allergic diseases

We found for the first time that IL-4 and IL-13 can induce periostin expression in airway epithelial cells.¹⁵ Since IL-4 and IL-13 are signature type 2 cytokines dominantly expressed in the inflamed sites of allergic diseases,¹⁶ it is reasoned that periostin is highly expressed in the subepithelial regions of many chronic inflammatory

diseases—asthma,¹ atopic dermatitis (AD),¹⁷ eosinophilic chronic sinusitis/chronic rhinosinusitis with nasal polyp (CRSwNP),^{18–21} and allergic conjunctivitis²²—as well. Thus far, to our knowledge, fibroblasts, epithelial cells, endothelial cells, and smooth muscle cells are known to produce periostin protein by stimulating IL-4 or IL-13.^{1,23–27} It is of note that IL-13-stimulated bronchial epithelial cells secrete periostin only from the basolateral side, not from the apical side.^{23,28} Although it is known that various stimuli other than IL-4 and IL-13 induce periostin expression (Figure 1),²⁹ TGF- β , histamine, and LIGHT (homologous to lymphotoxin, exhibits inducible expression, and competes with HSV glycoprotein D for binding to HVEM, a receptor expressed on T lymphocytes) are likely also important to induce periostin in the inflamed sites of allergic diseases.^{1,25,30} It is well known that STAT6 is a transcriptional factor critical for the IL-4 or IL-13 signals.³¹ We recently found that periostin is expressed by IL-13 by a *trans*-regulatory mechanism via SOX11, a member of the SOX (SRY-related HMG box) C family, downstream of STAT6, rather than by a *cis*-regulatory mechanism directly via STAT6.³²

3.2 | Mechanisms by which periostin causes allergic inflammation

It is also known that the actions of periostin as a matricellular protein are important in the pathogenesis of allergic diseases. We and others have shown that the epithelial/mesenchymal interaction and/or the immune cell/nonimmune cell interaction is important for periostin to exert its effects in the setting of inflammation. Regarding the epithelial/mesenchymal interaction, we have shown that periostin derived from fibroblasts acts on keratinocytes, inducing production of pro-inflammatory cytokines including thymic stromal lymphopoietin (TSLP) and IL-24 from keratinocytes (Figure 2A).^{17,26} TSLP acts on dendritic cells, driving type 2 inflammation, and IL-24 causes barrier dysfunction by downregulating filaggrin expression. Periostin activates NF- κ B, a transcriptional factor critical for inflammation in keratinocytes, which would lead to expression of these pro-inflammatory cytokines. We furthermore found that periostin derived from fibroblasts targets fibroblasts themselves in cooperation with IL-1 α derived from keratinocytes, activating NF- κ B followed by induction of pro-inflammatory cytokines such as IL-6 (Figure 2B).³³ Regarding the immune cell/nonimmune cell interaction, it has been reported that periostin acts on eosinophils and mast cells; periostin augments adhesion, superoxide anion (O_2^-) generation, TGF- β production, and migration in eosinophils^{34–36} and IgE-dependent degranulation response in mast cells (Figure 3).³⁷

In accordance with the *in vitro* studies, we showed that periostin plays a critical role in skin allergic inflammation using house dust mite (HDM)-painted mice.^{17,26,38} Features reminiscent of AD patients—skin swelling, epidermal hyperplasia, type 2 inflammation, and dermal fibrosis—were diminished in HDM-painted periostin-deficient mice. These results strongly support that periostin accelerates allergic inflammation, acting as a matricellular protein *in vivo*. In contrast, the results of applying periostin-deficient mice to the mouse model of asthma are controversial. It was initially

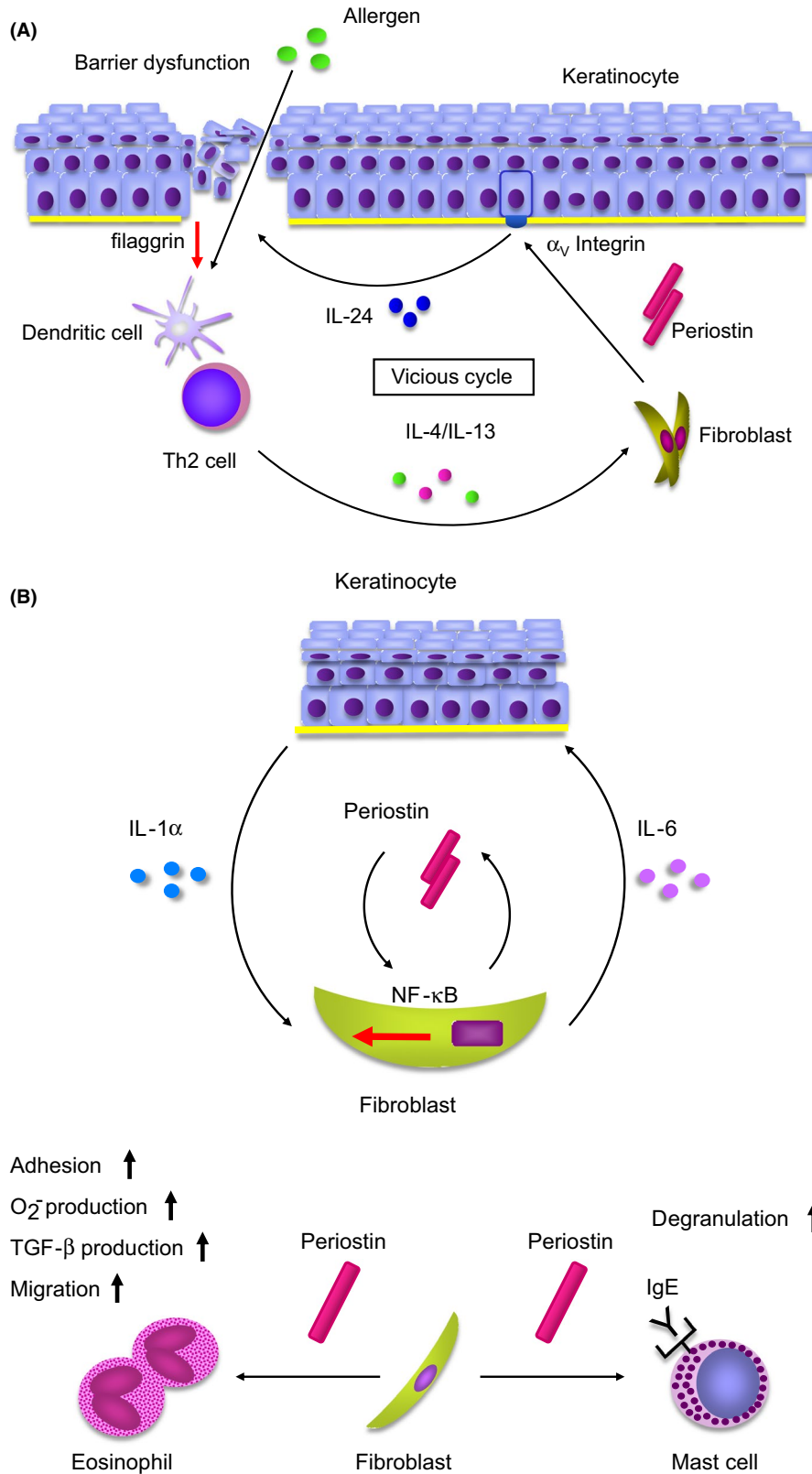


FIGURE 2 The epithelial/mesenchymal interaction causing allergic skin inflammation. A, IL-4 and IL-13 induce periostin expression in fibroblasts. Periostin acts on keratinocytes via α_v integrin activating NF- κ B in keratinocytes, followed by production of pro-inflammatory cytokines, including TSLP and IL-24 in keratinocytes. TSLP acts on dendritic cells driving type 2 inflammation, and IL-24 causes barrier dysfunction by downregulating filaggrin expression, respectively. B, Periostin derived from fibroblasts acts on the fibroblasts themselves via α_v integrin in cooperation with IL-1 α derived from keratinocytes. The stimuli of periostin and IL-1 α activate NF- κ B in fibroblasts, followed by induction of pro-inflammatory cytokines such as IL-6

FIGURE 3 The immune cell/nonimmune cell interaction causing allergic skin inflammation. Periostin acts on eosinophils enhancing their adhesion, superoxide anion (O_2^-) generation, TGF- β production, and migration, whereas periostin acts on mast cells upregulating the IgE-dependent degranulation response

reported that ovalbumin or *Aspergillus* challenge in periostin-deficient mice enhanced airway hyperresponsiveness (AHR), type 2 inflammation, and mucus production,^{39,40} whereas it was later shown that periostin deficiency or administration of neutralizing anti-periostin antibodies (Abs) decreased AHR, type 2 inflammation, and

mucus production in HDM-challenged mice.⁴¹ The reason for this discrepancy has been elusive, but it may be due to differences in experimental protocols. However, as we mention later in this article, we believe that periostin is a pro-inflammatory and pro-remodeling factor in asthma.

4 | CHARACTERISTICS OF PERIOSTIN AS A BIOMARKER FOR ALLERGIC DISEASES

4.1 | General characteristics of periostin as a biomarker

Periostin has emerged as a novel and useful biomarker of type 2 inflammation. Its usefulness as a biomarker for fibrotic diseases and cancers has been demonstrated as well as described elsewhere.^{42,43} The advantages of using periostin as a biomarker, among many mediators correlated with type 2 inflammation, are as follows.⁴⁴ (a) Periostin is increased in many pathological conditions in blood, urine, sputum/exhaled breath condensate (EBC), and tears. This suggests that periostin easily moves or is secreted from inflamed sites into various body fluids, although the precise mechanism of the moving or secretion still remains elusive. (b) The concentration of serum periostin is ~10 ng/mL, which is appropriate for accurately detecting any increase in the inflamed sites. If the serum concentration is high, as it can be with other ECM proteins such as fibronectin or vitronectin (~100 µg/mL), it would be difficult to find the increase in the inflamed area in the serum concentration. In contrast, if the serum concentration is low, as with cytokines (~10 pg/mL), it would be difficult to detect the serum concentration accurately.

The disadvantage of using periostin as a biomarker is that basal levels of serum periostin in childhood are high and vary depending on age. Fujitani et al⁴⁵ recently investigated age-related changes in serum periostin in allergic subjects and healthy children (Figure 4). Serum periostin levels were very high in infants, decreasing until age 7 and then increasing at least until age 15. This trend is consistent with other studies of children aged 2–11 years and from 6 to 11 years.^{46,47} Since the age-dependent change is consistent with the activity of bone metabolism, basal serum periostin would be derived mainly from bones. The basal levels of serum periostin during childhood and adolescence exceed 100 ng/mL; after bone growth stops, serum periostin drops to ~50 ng/mL.^{45,46} Fujitani et al⁴⁵ reported that healthy subjects showed higher serum periostin levels than allergic subjects until age 5 and that this relationship then reverses after age 5, within a narrow range. This suggests that the contribution of allergic conditions to serum periostin level cannot be evaluated in children under age 5 but it can be in children over age 5, within a narrow range, until bone growth stops. It is important to make use of the advantages of periostin as a biomarker in adults.

Estimation of serum periostin in allergic conditions sometimes differs among the reports. This could be ascribed to heterogeneity of allergic subjects as well as to the different periostin detection kits used.⁴⁸ We have established one periostin detection kit composed of two monoclonal anti-periostin antibodies (SS17B and SS18B), which has been provided by Shino-Test Corporation (Shino-Test assay). We compared the Shino-Test assay with the Elecsys® periostin assay provided by Genentech Inc, showing that these two assays have a significantly positive correlation ($r = 0.9236$, $P < 0.0001$) and that the absolute values are a little higher in the Shino-Test assay than in the Elecsys® periostin assay.⁴⁹ We also confirmed a good correlation between the Shino-Test assay and the Human Periostin/OSF-2

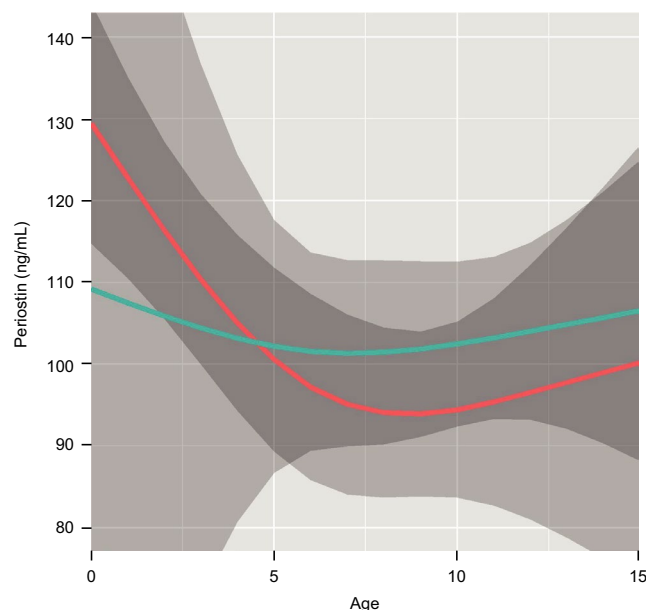


FIGURE 4 Relationship between age and serum periostin in nonallergic and allergy children. Serum periostin in each age group of nonallergic (red) and allergic (blue) children are depicted (modified based on Ref.⁴⁵). Gray areas indicate the confidence intervals for each group

DuoSet ELISA provided by R&D Systems (Figure S1, $r = 0.9319$, $P < 0.0001$). The standardization of periostin levels by different assay systems is needed to evaluate periostin values.

4.2 | Physiological factors affecting serum periostin

Body mass index (BMI) is known to be negatively correlated with serum periostin. We performed meta-analysis for association with periostin and BMI, type 2 biomarkers—eosinophil count, FeNO, and IgE—and predicted FEV₁, and compared asthma and control subjects (Data S1). Our meta-analysis showed a moderate association between serum periostin and BMI (fixed-effects model, -0.18 [-0.24 ; -0.12]; random-effects model, -0.18 [-0.24 ; -0.12], Figure 5). There are several reports showing that smoking downregulates serum periostin.^{49–51} Caswell-Smith showed that serum periostin changes during the day; it is higher in the morning than in the evening in both asthmatic and nonasthmatic subjects (asthma, 53.5 ± 13.6 ng/mL at 8 o'clock vs. 50.9 ± 13.4 ng/mL at 18 o'clock; nonasthma, 50.5 ± 13.0 ng/mL at 8 o'clock vs. 46.2 ± 11.5 ng/mL at 18 o'clock).⁵² Although some reports show differences of serum periostin in age and sex, the findings are not consistent among the reports.

4.3 | Asthma

It is widely accepted that asthma is a heterogeneous disease and that it is therefore important to characterize each endotype.⁵³ Although many attempts to categorize asthma into subgroups have been reported, the concept of dividing asthma based on type 2 inflammation (type 2 asthma vs. non-type 2 asthma) has been well supported⁵³ as

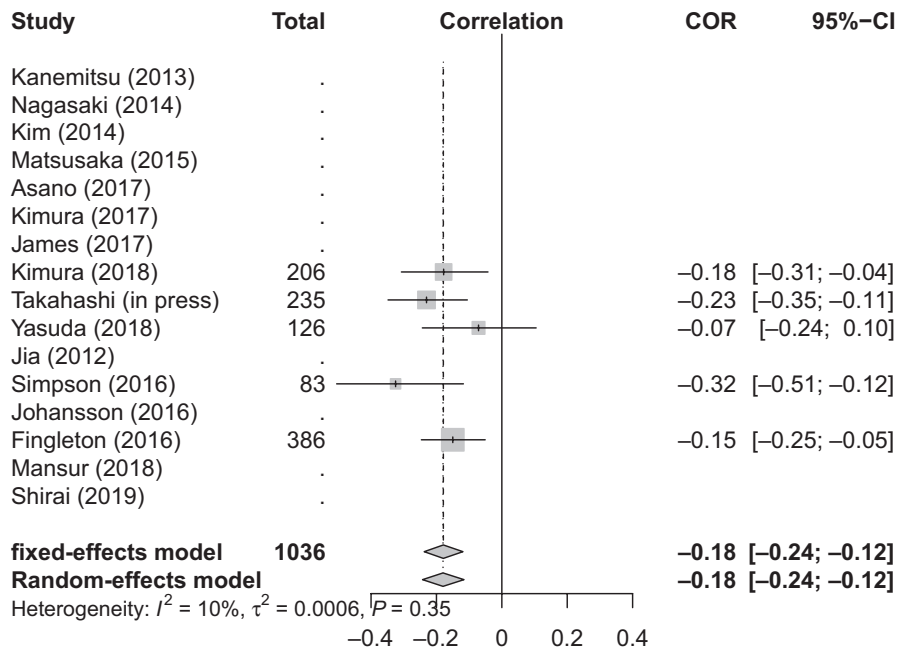


FIGURE 5 Meta-analysis of the association of serum periostin with BMI. The associations of serum periostin with BMI in each report and the values by the fixed-effects model and the random-effects model are depicted

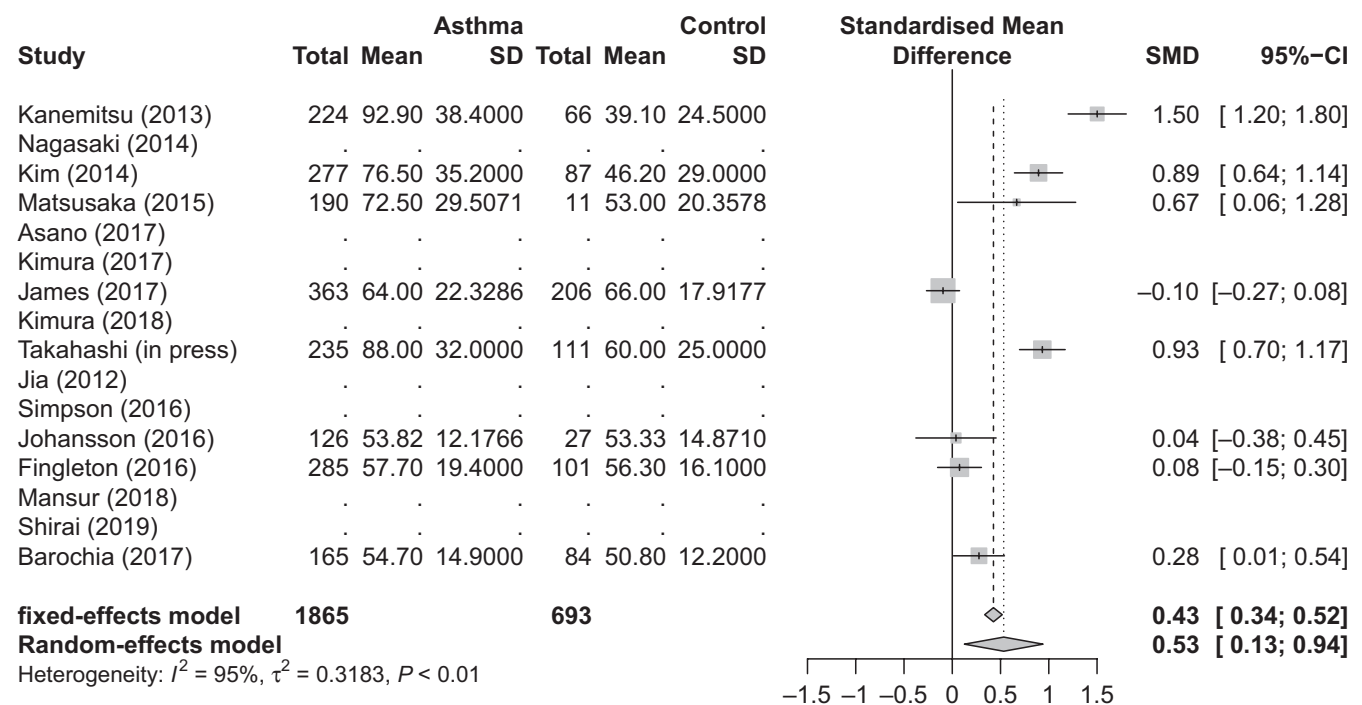


FIGURE 6 Meta-analysis of the comparison of serum periostin in asthma and control subjects. The comparisons of serum periostin in asthma and control subjects in each report and the values by the fixed-effects model and the random-effects model are depicted

it is useful for applying biologics against type 2 asthma—anti-IgE Ab, anti-IL-5/IL-5R Ab, and anti-IL-4R α Ab—to asthma patients. After periostin was identified as a signature gene of type 2 asthma,⁵⁴ a lot of attention has been paid to periostin as a novel type 2 biomarker.

Our meta-analysis shows that serum periostin is high in overall asthma patients compared with healthy subjects (fixed-effects model, 0.43 [0.34; 0.52]; random-effects model, 0.53 [0.13; 0.94],

Figure 6), although there is great heterogeneity in serum periostin among asthma patients ($I^2 = 95\%$), consistent with the notion that asthma is a heterogeneous disease. When we analyzed the association of serum periostin with other type 2 biomarkers—eosinophil count, FeNO, and total IgE—by meta-analysis, serum periostin was associated with all of these biomarkers moderately or weakly in order of eosinophil count (fixed-effects model, 0.29 [0.25; 0.33];

random-effects model, 0.30 [0.24; 0.35]), FeNO (fixed-effects model, 0.20 [0.14; 0.25]; random-effects model, 0.20 [0.12; 0.28]), and total IgE (fixed-effects model, 0.14 [0.09; 0.19]; random-effects model,

0.14 [0.06; 0.21], Figure 7). These type 2 biomarkers have different characteristics. For example, IL-5 is closely associated with maturation and proliferation of eosinophils. FeNO and IgE are produced in

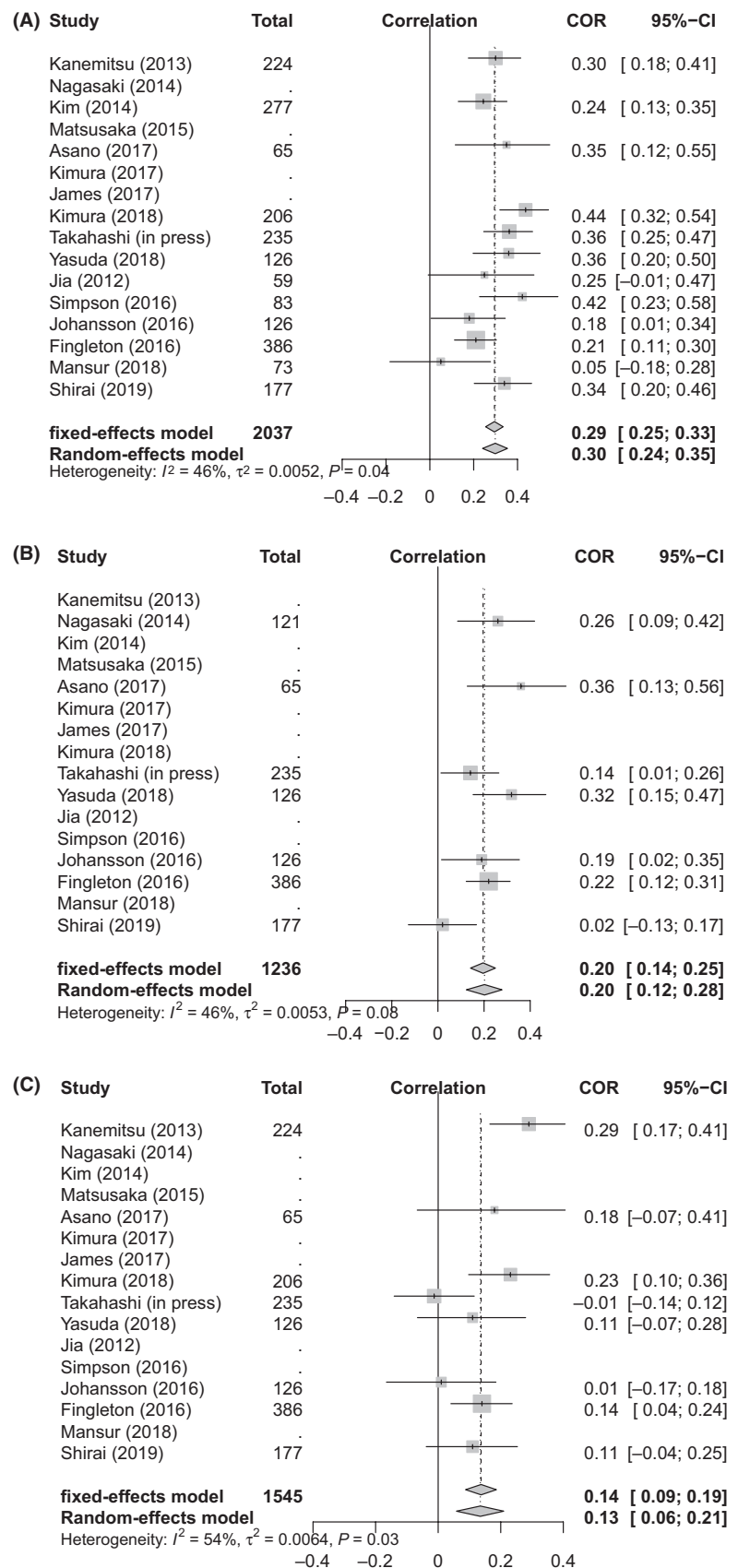


FIGURE 7 Meta-analysis of the association of serum periostin with type 2 biomarkers in asthma patients. The associations of serum periostin with eosinophil count (A), FeNO (B), and total IgE (C) in asthma patients in each report and the values by the fixed-effects model and the random-effects model are depicted

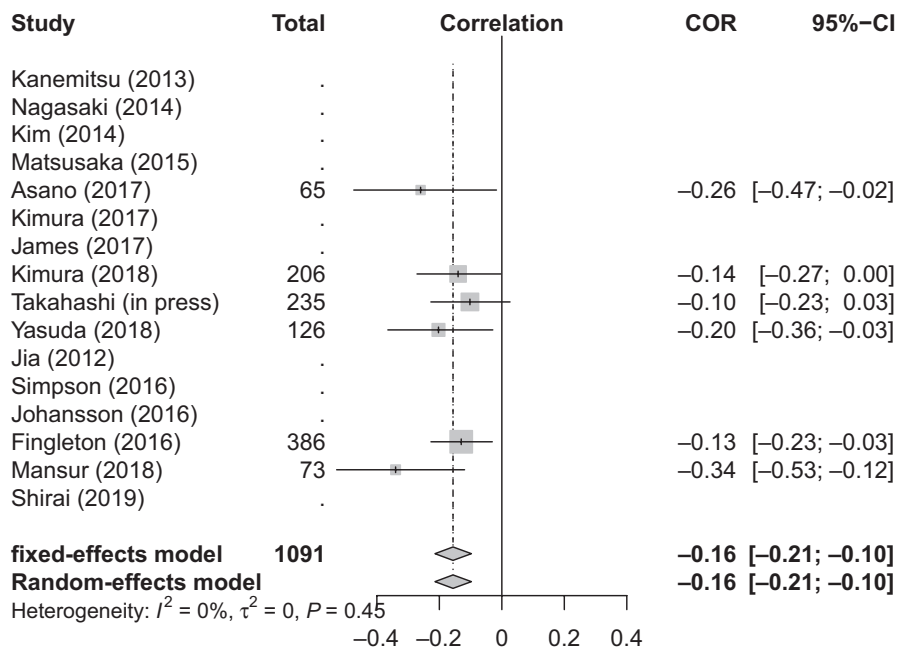


FIGURE 8 Meta-analysis of the association of serum periostin with lung function. The associations of serum periostin with predicted FEV₁ in asthma patients in each report and the values by the fixed-effects model and the random-effects model are depicted

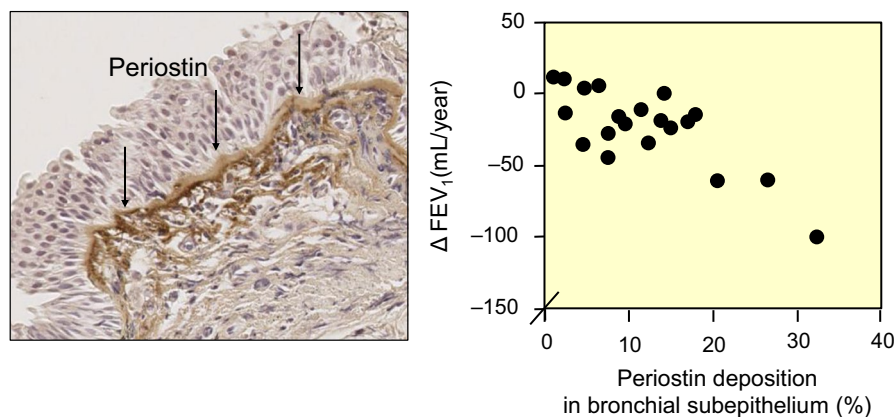


FIGURE 9 Correlation of the periostin deposition in bronchial subepithelium with decline of lung function in asthma patients. Periostin deposition in bronchial subepithelium was assessed by immunochemical analysis in the samples of 20 asthma patients. The samples were obtained by bronchial biopsy. The change in FEV₁ per year was estimated by spirometry during 20.3-y (SD, 1.3) follow-up. The correlation of periostin deposition with decline of lung function is depicted (modified based on Ref.⁵⁵)

epithelial cells and B cells, respectively, by stimulation of IL-4 or IL-13. Based on these differing characteristics, serum periostin behaves in some respects similar to but in others, differently from other type 2 biomarkers. Moreover, our meta-analysis shows that serum periostin is inversely correlated with predicted FEV₁ (fixed-effects model, -0.16 [-0.21; -0.10]; random-effects model, -0.16 [-0.21; -0.10], Figure 8). This would be because periostin is associated with fibrosis or remodeling of asthma. This notion is consistent with Kanemitsu's report that deposition of periostin in bronchial subepithelium in biopsy samples taken more than 20 years ago is well inversely correlated with decline of Δ FEV₁ (Figure 9).⁵⁵ Moreover, it was reported that serum periostin was correlated with thickening of bronchial walls on CT.⁵⁶ Existence of CRSwNP,⁵⁷⁻⁵⁹ aspirin intolerance,^{59,60} and sputum eosinophil count⁶¹⁻⁶³ are other important parameters associated

with serum periostin. Introducing inhaled corticosteroids (ICSs) to asthma patients promptly decreased FeNO levels, whereas serum periostin went down slowly.⁶⁴ This would suggest that ICSs improve superficial inflammation by decreasing FeNO secreted from epithelial cells, whereas the inflammation of deep layers remains, so that periostin deposited in subepithelial regions would not change so quickly. From this point of view, we may say that serum periostin is a "chronic" type 2 biomarker, whereas FeNO is an "acute" type 2 biomarker.⁶⁴

It is important to predict the efficacy of biologics for allergic diseases by certain biomarkers. As we have mentioned, it was reported that a high-periostin group, but not a low-periostin group, showed good efficacy for improving FEV₁, but not the ACQ5 score or exacerbation rate, by lebrikizumab, a neutralizing anti-IL-13 antibody, in a phase 2 trial.² In the subsequent phase 2b studies (the LUTE and

VERSE studies), lebrikizumab reduced the exacerbation rate in addition to improving lung functions in a periostin-high group.⁶⁵ However, in its phase 3 trial (the LAVOLTA I and II studies), the subjects were grouped into eosinophil-high or periostin-high patients. Reduction of the exacerbation rate by lebrikizumab reached statistical significance in the LAVOLTA I study, but not in the LAVOLTA II study.⁶⁶ Of note is that in both the LAVOLTA I and II studies, lebrikizumab reduced exacerbations of asthma in periostin-high asthma patients with statistical significance, suggesting that these studies did not impair the usefulness of periostin to predict the efficacy of lebrikizumab for asthma. Tralokinumab, another anti-IL-13 Ab, also showed efficacy to improve FEV₁, but not the exacerbation rate or ACQ-6/AQLQ scores in its phase 2b study in a periostin-high group.⁶⁷ In this trial, dipeptidyl peptidase 4 (DPP4), another type 2 biomarker, predicted improvement of FEV₁ and ACQ6/AQLQ scores by tralokinumab. In its phase 3 trial (the STRATOS 1 and 2 studies), although FeNO was chosen as an optimal biomarker to stratify tralokinumab-effective patients, sufficient efficacy was shown in the STRATOS 1 study, but not in the STRATOS 2 study.⁶⁷ Dupilumab, a neutralizing anti-IL-4R α Ab inhibiting both the IL-4 and IL-13 signals, showed good efficacy in reducing the exacerbation rate and improving FEV₁ in its phase 3 trial.⁶⁸ Serum periostin could stratify patients to predict efficacy of dupilumab in improving FEV₁; however, FeNO showed better ability. Moreover, serum periostin levels were not useful for predicting the reduction of the exacerbation rate by dupilumab. Regarding other biologics, it has been demonstrated that serum periostin is to some extent useful to predict efficacy of omalizumab, anti-IgE Ab, although a single measurement of serum periostin is not enough to do it.^{69,70}

Remodeling is an important factor in resistance to ICSs.⁷¹ Several reports have shown that serum periostin is high in asthma patients resistant to ICSs, particularly in eosinophil-dominant groups.^{49,59,72,73} Moreover, Kato et al⁷⁴ demonstrated that periostin-high asthma patients showed a high frequency of exacerbation after tapering ICSs. These characteristics would indicate that periostin is a remodeling or chronic type 2 biomarker.

It has been reported that periostin is measurable in induced sputum or EBC.^{63,75,76} Periostin in sputum or EBC is particularly high in severe and type 2 asthma or in eosinophil-dominant asthma.^{63,76} Since periostin in sputum or EBC directly reflects airway inflammation, as a biomarker it would be more or perhaps differently useful compared to serum periostin.

Serum periostin in children is relatively higher than adults, although under age 5, high periostin in allergic subjects cannot be observed, as mentioned earlier. Accordingly, asthmatic subjects of school age showed only slightly higher serum periostin levels than controls, with relatively high levels in both groups compared with adults,^{77,78} whereas there was no difference between asthma subjects and control under age 3.⁷⁹

4.4 | Atopic dermatitis

Although type 2 inflammation is dominant in AD pathogenesis, AD is thought to be a heterogeneous disease⁸⁰; there exist type 2 and

non-type 2 AD, and involved inflammation is different at different stages. Periostin is highly expressed in the dermis of the inflamed region of overall AD patients.^{17,81,82} This is mainly attributed to the actions of IL-4 and/or IL-13 being highly expressed in the lesions on fibroblasts. Yang et al³⁰ showed that histamine, a critical mediator for the pathogenesis of AD, can also induce periostin in fibroblasts. Keratinocytes can produce periostin to a lesser extent compared to fibroblasts in response to IL-4/IL-13 or LIGHT.^{25,26} Released periostin acts on keratinocytes, inducing production of pro-inflammatory cytokines such as TSLP or IL-24, followed by activation of DCs or barrier dysfunction, respectively, leading to the vicious cycles of AD.^{17,26} Moreover, periostin acts on fibroblasts as well, inducing pro-inflammatory cytokines such as IL-6 and matrix proteins such as type 1 collagen.^{30,33} Thus, periostin plays a critical role in the pathogenesis of AD as a matricellular protein.

Serum periostin is high in adult AD patients^{17,82-84} as well as in child AD patients,^{85,86} although the window in children is narrower compared to adults, as mentioned above. Serum periostin is correlated with disease severity or SCORAD and with several biomarkers, such as TARC, LDH, IgE, and eosinophil count.^{82,86} Serum periostin is higher in patients with extrinsic (vs. intrinsic) AD, erythroderma type (vs. scaly erythema), lichenification, excoriation, or *Staphylococcus aureus*-positive.^{82,83,86} Moreover, serum periostin is decreased by conventional treatment for AD such as topical corticosteroids or immunosuppressive agents or by dupilumab, an inhibitor for IL-4/IL-13 signals.^{82,84} Dupilumab showed good efficacy for improving IGA scores and a 75% reduction in the EASI score (EASI-75) for two phase 3 trials, SOLO 1 and SOLO 2⁸⁷ and was commercialized in 2017 (DUPIXENT®). Although dupilumab showed enough efficacy compared to placebo for moderate-to-severe AD patients without stratification, it is of particular interest to examine whether stratification by some type 2 biomarker, including serum periostin, can make more precisely the efficacy of dupilumab.

4.5 | Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is a heterogeneous group and is classified by a combination of endotypes (type 2 inflammation vs. non-type 2 inflammation) and phenotypes (existence of nasal polyp and asthma risk).⁸⁸ This classification is important for selecting treatments for CRS patients: glucocorticoids, antibiotics, and biologics now under development. It has been of interest to learn whether periostin can be a biomarker useful for stratifying CRS patients. Initial studies showed that periostin was highly expressed overall in the lesions of CRS patients at both mRNA and protein levels.¹⁸⁻²¹ High deposition of periostin has been observed in the subepithelium in nasal polyps, with the highest in the border of the epithelium.^{18,89,90} These findings are consistent with the notion that fibroblasts would be the main periostin-producing and periostin-targeted cells in CRS. Actually, it has been demonstrated that periostin enhances production of VEGF, RANTES, eotaxin-2, and ECMs such as collagen 1 and fibronectin and expression

of α -SMA in nasal fibroblasts, which would be one mechanism by which periostin is involved in the pathogenesis of CRS.^{89,91} Expression of periostin in inflamed sites is reported to be correlated with a number of factors—disease severity, existence of nasal polyps, fibrosis, tissue eosinophil count, IL-5 level, IL-13 level, formation of extracellular eosinophilic trap by *Staphylococcus aureus*, and response to glucocorticoids—suggesting that periostin is a biomarker reflecting type 2 inflammation and fibrosis in CRS.^{90–96}

It has been reported that serum periostin is associated with disease severity, existence of nasal polyps, tissue and blood eosinophilia count, responses to glucocorticoids, omalizumab, and mepolizumab, and postoperative recurrence.^{90,97–100} These results suggest that serum periostin is useful for stratifying CRS patients based on endotypes and has the potential to predict efficacy of biologics for CRS now under development. It should be noted that Ninomiya et al⁹⁰ have demonstrated that the cutoff value of 115.5 ng/mL indicates a significant difference in postoperative recurrence, which would be useful information for managing patients and considering how best to use biologics. Moreover, Jonstam et al⁹⁸ have shown that the cutoff value of 48.5 ng/mL predicts the presence of IL-5–positive CRS with 93.5% sensitivity and 62.5% specificity, suggesting that serum periostin has the potential to predict the efficacy of IL-5 or IL-5R antagonists, in combination with eosinophil count.

4.6 | Allergic conjunctivitis

In spite of its high prevalence, allergic conjunctivitis is often underdiagnosed and undertreated.¹⁰¹ Moreover, chronic types of allergic conjunctivitis—atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC)—need to be appropriately treated as they can be accompanied by corneal changes, tissue remodeling, and fibrosis such as corneal ulcers and the formation of giant papilla, which can lead to loss of vision.^{102,103} Therefore, development of a novel biomarker to diagnose allergic conjunctivitis and accurately estimate its severity has been long awaited.

We have reported on the usefulness for this purpose of measuring tear periostin in ocular allergic diseases.²² Patients with seasonal allergic conjunctivitis (SAC), a very common type of allergic conjunctivitis, showed clear increase in tear periostin (median, 12.2 ng/mL) compared to healthy donors (0.2 ng/mL). Patients with chronic types of allergic conjunctivitis, AKC and VKC, showed much higher tear periostin levels (AKC, 444.0 ng/mL; VKC, 67.0 ng/mL) than SAC. Tear periostin levels were positively correlated with complications of AKC such as papilla formation or corneal damage. Moreover, in some AKC patients, topical treatment with immune suppressants decreased tear periostin and improved clinical features, although there is a possibility that the decreased tear periostin could be ascribed to indirect effects of immune suppressants by improving AD. The importance of periostin in the pathogenesis of allergic conjunctivitis has been very recently shown by applying periostin-deficient mice to ragweed-induced experimental allergic conjunctivitis (RW-EAC).¹⁰⁴ The number of eosinophils in the conjunctival tissue of RW-EAC decreased by about 90% in periostin-deficient mice compared

with wild-type mice, in association with significantly reduced CCL5/RANTES expression in the tissue. These results suggest the utility of measuring tear periostin in diagnosing allergic conjunctivitis and evaluating its disease activity as well as in monitoring the efficacy of treatments. It should be noted that tears can be easily collected; diagnosis of allergic conjunctivitis and evaluation of its activity can be performed qualitatively rather than quantitatively because of the wide range of differences between AKC/VKC, SAC, and control.

5 | CONCLUSION AND FUTURE DIRECTIONS

In this article, we describe the roles of periostin in allergy and the utility and potential of periostin in developing diagnostics and therapeutic agents against allergic diseases. This field has developed dramatically in these past several years. However, several problems involving biomarkers have remained unresolved. (a) Eight variants in the C-terminal region of periostin have been officially reported (<https://www.ncbi.nlm.nih.gov/gene/10631>). However, almost nothing is known about the expression profile of each of these variants in pathological conditions including allergic diseases, and there is no system available to differentiate each variant as a biomarker. (b) Periostin in body fluids has greater potential as a biomarker than serum periostin, because the former would directly reflect local inflammation. Actually, it has been reported that measuring periostin in sputum/EBC and in tears has different usefulness from that of serum periostin.^{22,63,76} More information is needed about periostin in body fluids, for which we need suitable detection systems. (c) Many studies have suggested that a single biomarker or a single cutoff value is not enough to stratify patients, particularly as to the efficacy of molecularly targeted drugs. For this purpose, it is important to investigate the usefulness of combinations of biomarkers and/or the sequential cutoff values of biomarkers. Moreover, given that deficiency or inhibition of periostin protects against various periostin-related diseases including allergic diseases, periostin is a potential target in developing therapeutic drugs for these diseases. There are two strategies to block the functions of periostin: targeting periostin itself and targeting its receptor, integrin. Periostin-targeting drugs may give us benefits different from other anti-allergy drugs. It is hoped that in the near future, these studies will give us a new and broader understanding of the pathogenesis of allergic diseases, yielding useful diagnostics or therapeutic agents against them.

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CONFLICTS OF INTEREST

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ORCID

Kenji Izuhara  <https://orcid.org/0000-0002-6983-907X>

Satoshi Nunomura  <https://orcid.org/0000-0002-9315-4185>

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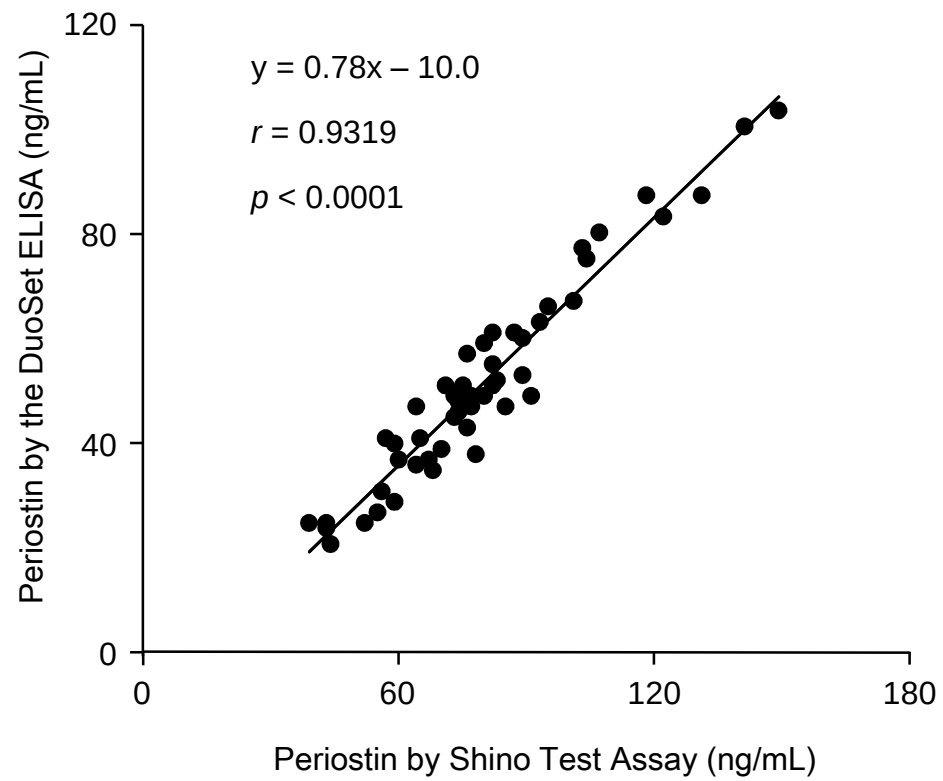
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.



Izuhara *et al*, Supplementary Figure 1

Supplementary Data

The meta-analysis was performed calculating the weighted standardized mean difference with Hedges' g bias correction for continuous outcomes and the weighted Fisher's z transformation of correlations. Both a fixed effect and a random effects model by based on the DerSimonian-Laird method were applied. For continuous outcomes, the median, the first, and the third quartiles were converted to the mean and the standard deviation by using their formula.¹⁰⁵ The data accessed by the Shino-test assay^{49-51, 57-60, 72, 106, 107} and by the Elecsys[®] periostin assay^{61, 62, 108-112}, obtainable on the internet, were used for the analyses.