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REVIEW ARTICLE

Review Series: Periostin

# Periostin in Allergic Inflammation

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## ABSTRACT

Periostin, an extracellular matrix protein belonging to the fasciclin family, has been shown to play a critical role in the process of remodeling during tissue/organ development or repair. Periostin functions as a matricellular protein in cell activation by binding to their receptors on cell surface, thereby exerting its biological activities. After we found that periostin is a downstream molecule of interleukin (IL)-4 and IL-13, signature cytokines of type 2 immune responses, we showed that periostin is a component of subepithelial fibrosis in bronchial asthma, the first formal proof that periostin is involved in allergic inflammation. Subsequently, a great deal of evidence has accumulated demonstrating the significance of periostin in allergic inflammation. It is of note that in skin tissues, periostin is critical for amplification and persistence of allergic inflammation by communicating between fibroblasts and keratinocytes. Furthermore, periostin has been applied to development of novel diagnostics or therapeutic agents for allergic diseases. Serum periostin can reflect local production of periostin in inflamed lesions induced by Th2-type immune responses and also can predict the efficacy of Th2 antagonists against bronchial asthma. Blocking the interaction between periostin and its receptor, $\alpha_v$ integrin, or down-regulating the periostin expression shows improvement of periostin-induced inflammation in mouse models or in *in vitro* systems. It is hoped that diagnostics or therapeutic agents targeting periostin will be of practical use in the near future.

## KEY WORDS

allergy, atopic dermatitis, bronchial asthma, inflammation, periostin

## *INTRODUCTION*

A typical inflammatory response is composed of four stages: 1) invasion by microbes or damage of tissues; 2) sensing infection or tissue damage by the immune system; 3) production of mediators including cytokines, bioactive amines, and eicosanoids by the immune system; and 4) effects of the mediators on target tissues.[1] Once the invaded microbes are eliminated or the damaged tissues are repaired, the inflammatory responses are terminated. However, if the inflammatory response persists, a chronic inflammatory state will ensue. Chronic inflammatory responses often cause tissue changes including remodeling, fibrosis, and metaplasia, which lead not only to the decline or loss of normal tissue functions, but also to the onset of new clinical symptoms.[1]

Since allergic diseases such as bronchial asthma and atopic dermatitis (AD) triggered by allergen invasions usually become chronic, the affected lesions in patients with these diseases present histologically with chronic inflammation. Asthma patients show mucus metaplasia, smooth-muscle hypertrophy, and enhanced deposits of subepithelial matrix proteins, termed "airway remodeling".[2] These histological changes are thought to lead to the airflow limitations and airway hyper-responsiveness (AHR) found in these patients. In AD patients, epidermal changes are evident, including epidermal thickness called acanthosis and hyper-/parakeratosis.[3] Although the exact pathological role of acanthosis remains unclear, we speculate that it provides a basis for supplying massive proinflammatory mediators from keratinocytes.[4,5]

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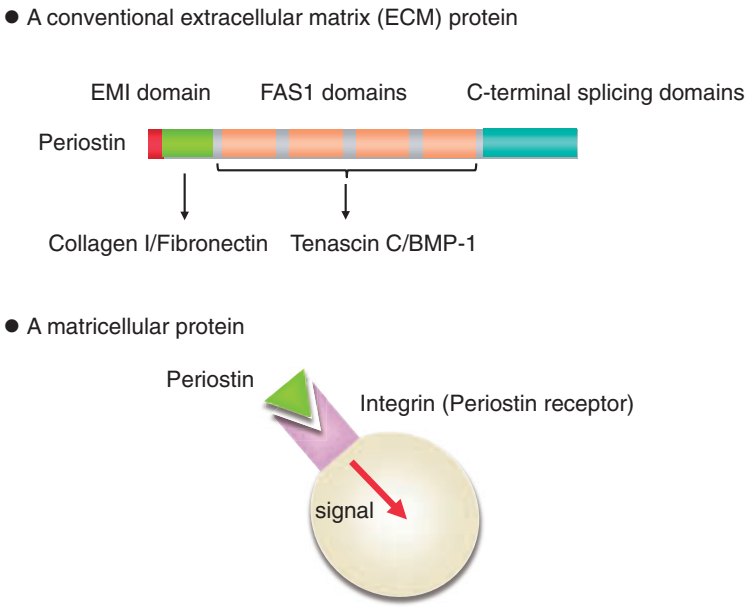


**Fig. 1** Two faces of periostin. Periostin has two faces: a conventional ECM protein (upper panel) and a matricellular protein (lower panel). As a conventional ECM protein, periostin is important for maintaining tissue/organ structure or generating fibrosis, whereas it is important for cell activation as a matricellular protein. Periostin is composed of an EMI domain at the N terminus, four tandemly aligned FAS1 domains in the middle, and splicing domains at the C terminus. ECM proteins or a proteinase that can bind to the EMI domain or the FAS1 domains are depicted. In contrast, periostin binds to integrin molecules on cell surface transducing intracellular signals.

Periostin, an extracellular matrix (ECM) protein, has recently emerged as a novel mediator in chronic states of allergic diseases and plays an important role in tissue remodeling in allergic inflammation. In this review article, we focus on the significance and clinical application of periostin in allergic inflammation.

## CHARACTERISTICS OF PERIOSTIN

Periostin, originally termed osteoblast-specific factor 2, is an ECM protein of 93.3 kDa in size.[6] It belongs to the fasciclin family on its homology to fasciclin 1 (FAS1). Periostin is composed of an EMI domain at the N terminus, four tandemly aligned FAS1 domains in the middle, and splicing domains at the C terminus (Fig. 1). The EMI domain is able to bind to collagen I and fibronectin,[7-9] whereas the FAS1 domains can bind to tenascin-C and bone morphogenetic protein (BMP)-1.[7,8,10] These abilities of periostin as an ECM protein to interact extracellularly with other ECM proteins or proteinase (BMP-1) are assumed to be important in maintaining tissue structure or generating fibrosis.

Since periostin was first isolated from a mouse osteoblast cell line in 1993,[11] our understanding of periostin biology began in osteology.[6,12] It has turned out that periostin contributes critically to bone development/remodeling and bone strength. Expression of periostin is up-regulated during fracture repair or in response to mechanical stress when bone development or remodeling is required. Periostin plays its part by regulating collagen crosslinking and fibrillogenesis by binding to BMP-1 or by binding to Notch 1. Periostin biology has then been extended to the field of cardiology.[6,13] It has been shown that periostin plays a central role in cardiovascular differentiation during *in utero* development of the cardiac valves and fibrous heart skeleton. Even in the postnatal stage, when expression of periostin is low compared to the embryonic stage, periostin expression is rapidly up-regulated in response to insult/injury and is involved in cardiac remodeling. Furthermore, we and others recently showed that upon skin injury, periostin is transiently expressed in granulation tissues and accelerates cutaneous wound repair.[14-16] All of these findings suggest that periostin is a "remodeling" molecule. Thus the significance of periostin in mesenchymal remodeling in various healthy and pathological states has been established.

As periostin biology was becoming better understood, it was revealed that periostin has another face,

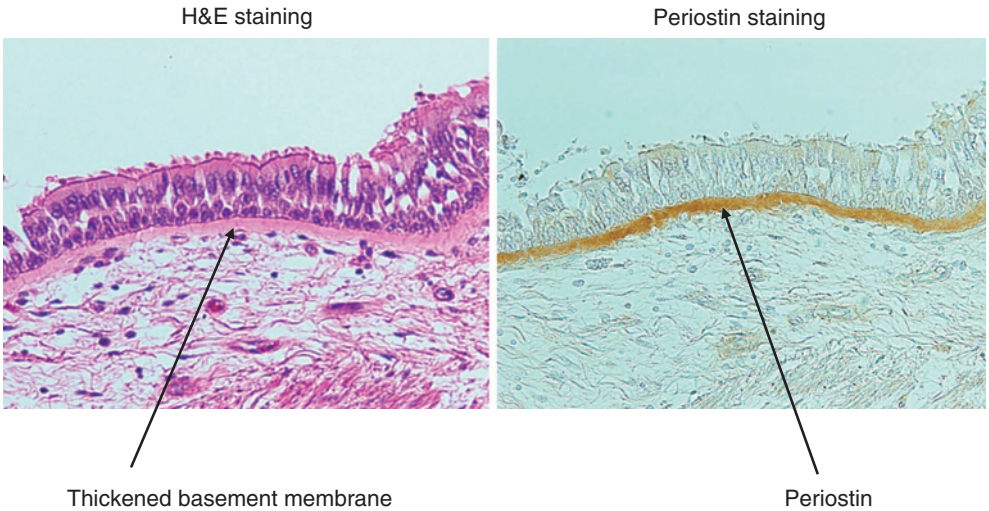


**Fig. 2** Expression of periostin in asthma patients (cited from Ref. 32). The histochemical localization of periostin in asthma patients is depicted. The left and right panels show bronchial tissues from an asthma patient in H&E staining (left panel) and in immunostaining of periostin (right panel). Periostin in the right panel is stained in brown and is localized in the thickened basement membrane in asthma patients.

as a type of ECM protein called a matricellular protein (Fig. 1). Matricellular proteins are defined as ECM proteins binding to their receptors on cell surface and functioning in cell activation rather than in maintenance of tissue structure.[13,17,18] Several integrins—such as $\alpha_V\beta_1$,[19,20] $\alpha_V\beta_3$,[20,21] $\alpha_V\beta_5$,[20,21] $\alpha_6\beta_4$,[22] and $\alpha_M\beta_2$[23]—have been reported to be periostin receptors. Binding of periostin with these integrin molecules activates signal pathways, including FAK,[22,24] PI3-kinase,[19,20,22,25] Akt,[22,26] ERK,[15] NF-κB,[4,14] and STAT3.[15] Activating these signal pathways is important for periostin to exert its biological activities as a remodeling molecule.

## DISCOVERY OF PERIOSTIN AS A NOVEL MEDIATOR IN BRONCHIAL ASTHMA

Periostin was discovered as a novel mediator in allergic diseases in the course of elucidating the pathogenesis of bronchial asthma. The significance of interleukin (IL)-13, a type-2 cytokine, in the pathogenesis of bronchial asthma was established around 2000 based on analyses of model mice and of susceptible genes of asthma.[27,28] In particular, bronchial epithelial cells are an important target for IL-13 to cause AHR, a typical feature of asthma.[29] To elucidate the effects of IL-13 on human bronchial epithelial cells, we comprehensively identified IL-13-inducible genes using the DNA microarray method, finding that periostin is one of the highly expressed genes.[30] The induction of periostin by IL-13 is more than ten-fold by quantitative PCR analysis, and IL-4 has the same ability to induce periostin as IL-13.

To investigate involvement of periostin in the pathogenesis of bronchial asthma, we generated antibodies against periostin and performed immunohistochemical analyses.[7,31] We found that periostin is deposited on the thickened basement membrane in asthma patients (Fig. 2). It is known that subepithelial fibrosis, a cardinal feature of bronchial asthma, is thickening of the lamina reticularis, in which collagens I, III, and V; fibronectin; and tenascin-C are deposited beneath the basal lamina (the "true" basement membrane).[32,33] The localization of periostin is the same as that of these ECM proteins, suggesting that periostin is a novel component of subepithelial fibrosis in bronchial asthma. Deposition of periostin can be observed in the subepithelial areas of model mice in an IL-4- or IL-13-dependent manner.[7] Interestingly, fibroblasts are likely to be the major source of periostin, although we first found periostin as an IL-13-inducible gene in airway bronchial epithelial cells. Upon stimulation of IL-4 or IL-13, airway epithelial cells express periostin at mRNA level, but not at protein level, whereas fibroblasts can secrete periostin proteins. This was the first formal proof that periostin is involved in bronchial asthma, and moreover in allergic inflammation.

Subsequently, Fahy and colleagues in UCSF confirmed the up-regulated expression of periostin in asthma patients.[34,35] Importantly, asthma patients can be classified into "Th2-high" and "Th2-low" asthma in which expression of IL-13 and IL-5 is high and low, respectively. Periostin is a signature molecule of "Th2-high" asthma together with chloride channel regulator 1 and serpin peptidase inhibitor, clade B, member 2.[35] This finding established the basis for the application of periostin as a biomarker of Th2-high asthma. The pathological role of periostin in

**Table 1** Periostin-involving inflammatory diseases

| | Reference(s) |
|---|---|
| • Allergic diseases | |
| Bronchial asthma | 32, 33 |
| Atopic dermatitis | 4 |
| IgG4-related sclerosing sialadenitis | 38 |
| Eosinophilic otitis media | 39 |
| Allergic rhinitis and chronic rhinosinusitis | 40 |
| • Non-allergic diseases | |
| Idiopathic pulmonary fibrosis | 43 |
| Drug-induced pulmonary fibrosis | 44 |
| Scleroderma | 45 |
| Proliferative diabetic retinopathy | 45, 46 |
| Bone marrow fibrosis | 48 |

asthma still remains controversial; several initial studies using periostin-deficient mice showed that periostin acts as a protective molecule against allergic airway inflammation.[36,37] However, Bentley *et al.* recently reported that periostin accelerates allergic airway inflammation using periostin-deficient mice and neutralizing antibodies against periostin (American Thoracic Society International Conference 2013). More studies are needed to elucidate whether periostin exerts a beneficial or deleterious effect on the onset of bronchial asthma.

## THE FUNCTIONAL ROLE OF PERIOSTIN IN ALLERGIC INFLAMMATION

After we demonstrated periostin's involvement in the pathogenesis of bronchial asthma, we surveyed inflammatory diseases for potential involvement of periostin, finding that periostin is involved in other allergic diseases such as AD,[4] IgG4-related sclerosing sialadenitis,[38] eosinophilic otitis media,[39] and allergic rhinitis and chronic rhinosinusitis[40] (Table 1). These results are plausible considering that periostin is a downstream molecule of IL-4 or IL-13, highly expressed cytokines in allergic diseases. Yamaguchi *et al.* and Ohta *et al.* describe the involvement of periostin in dermatologic or otolaryngologic diseases in the same issue of this journal.[41,42] It is of note that we also found involvement of periostin in non-allergic inflammatory diseases such as idiopathic or drug-induced pulmonary fibrosis,[43,44] scleroderma,[45] proliferative diabetic retinopathy[46,47] and bone marrow fibrosis.[48] Additionally, various malignant tissues show high expression of periostin.[49,50] Since it is known that various factors other than IL-4 and IL-13—transforming growth factor β 1[51] and 3[52], fibroblast growth factor 1,[53] angiotensin II,[53] BMP-2,[54] and platelet-derived growth factor,[55]—can induce periostin expression, these or unknown factors may contribute to up-regulated expression of periostin in non-allergic inflammatory states.

Although, as we mentioned earlier, the role of periostin in the pathogenesis of bronchial asthma is still unclear, we proposed how periostin exacerbates and persists allergic inflammation in skin tissues based on the analyses of periostin-deficient mouse and three-dimensional organotypic coculture system using keratinocytes and fibroblasts (Fig. 3).[4] Invasion of allergens into hosts triggers type 2 immune responses. IL-4 and IL-13, type 2 cytokines, stimulate production of periostin in fibroblasts. Periostin acts on $\alpha_v$ integrin on keratinocytes inducing production of proinflammatory cytokines including TSLP. The proinflammatory cytokines from keratinocytes then amplify type 2 immune responses. Thus, IL-4/IL-13, periostin, and proinflammatory cytokines including TSLP, compose a vicious circle in allergic skin inflammation. This scheme shows that periostin plays a critical role in amplification and persistence of allergic inflammation by communicating between fibroblasts and keratinocytes. It is of note that fibrosis that was believed before to be the end result of inflammation can be a platform for the onset of inflammation.

We then examined the molecular mechanism of how periostin causes epidermal thickness (acanthosis) and hyper-/parakeratosis in allergic skin inflammation by extending the analyses using the three-dimensional organotypic coculture system (Fig. 4).[56] IL-1α is a cytokine secreted constitutively from keratinocytes critical for proliferation and differentiation of keratinocytes. Periostin secreted from fibroblasts synergistically acts on fibroblasts with IL-1α inducing production of IL-6 by activation of the NF-κB pathway. IL-6 secreted from fibroblasts is another cytokine critical for proliferation and differentiation of keratinocytes. Thus, an autocrine loop of periostin is involved in the regulation mechanism of keratinocyte proliferation and differentiation, together with a paracrine loop composed of IL-1α and IL-6. Periostin would tune the magnitude of keratinocyte proliferation and differentiation by interacting with the paracrine IL-1α/IL-6 loop.

These findings demonstrate the significance of epithelial cells and fibroblasts as targets of periostin in allergic skin inflammation. Several reports support this concept.[14-16,25,44,47] Furthermore, periostin targets eosinophils, accelerating their adhesion to ECM proteins.[57] Thus, periostin plays an important role in allergic inflammation by acting on epithelial cells, fibroblasts, eosinophils and possibly other undetermined immune and non-immune cells.

## USEFULNESS OF PERIOSTIN AS A BIOMARKER IN ALLERGIC DISEASES

Considering the findings that periostin is highly expressed in affected regions of various inflammatory diseases, it is reasonable to assume that serum periostin is a biomarker reflecting local production of periostin. Measurement of serum periostin has ad-

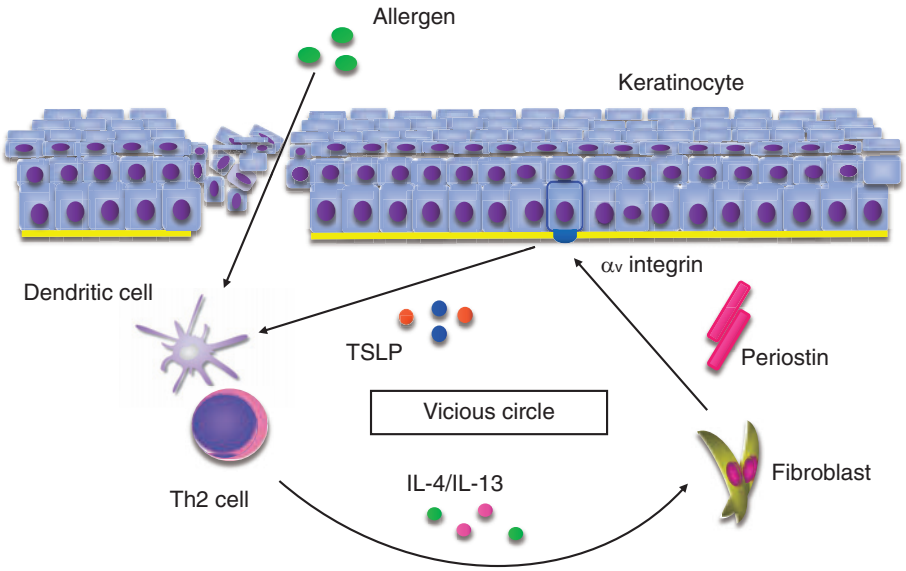


**Fig. 3** Vicious circle composed of IL-4/IL-13, periostin, and TSLP, in allergic skin inflammation (modified from Ref. 4). The vicious circle composed of IL-4/IL-13, periostin, and TSLP in allergic skin inflammation is depicted. Invasion of allergens into hosts triggers type 2 immune responses. IL-4 and IL-13, type 2 cytokines, stimulate production of periostin in fibroblasts. Periostin acts on $\alpha_v$ integrin on keratinocytes inducing production of proinflammatory cytokines, including TSLP. The proinflammatory cytokines from keratinocytes then amplify type 2 immune responses.

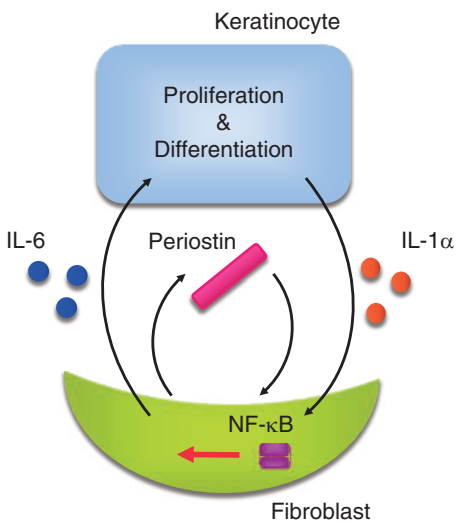


**Fig. 4** Molecular mechanism of epidermal thickness (acanthosis) and hyper-/parakeratosis by periostin in allergic skin inflammation (modified from Ref. 56). An autocrine loop of periostin and a paracrine loop composed of IL-1α and IL-6 are involved in the regulatory mechanism of keratinocyte proliferation and differentiation. Periostin and IL-1α secreted from fibroblasts and keratinocytes, respectively, synergistically act on fibroblasts inducing production of IL-6 by activating the NF-κB pathway. IL-6 secreted from fibroblasts is critical for proliferation and differentiation of keratinocytes.

vantages in being a biomarker for various inflammatory diseases for two reasons. First, periostin is likely to move easily from the affected lesions to vessels. Second, since basal serum levels of periostin are relatively low (~50 ng/ml) compared to other ECM proteins such as fibronectin or vitronectin (200-300 μg/ml), up-regulated local production of periostin in the affected lesions can be easily reflected to serum periostin levels. Thus far, several commercial or non-commercial ELISA kits for periostin are available. Since the detection limit in the ELISA kit that we developed is very low (~20 pg/ml), we can decrease the effects of other serum proteins on the periostin analysis using this kit.

Genentech developed serum periostin into a surrogate marker for Th2-high asthma based on the finding that periostin is a signature molecule of Th2-high asthma, which is characterized by higher AHR, serum IgE, eosinophilic inflammation, subepithelial fibrosis, and epithelial mucins compared to Th2-low asthma.[35,58] Since IL-4 and IL-13 are critical molecules for the onset of bronchial asthma in the model mice, several antagonists against IL-13 and/or IL-4 have been developed as anti-asthma agents; however, some clinical trials have been disappointing or not sufficiently satisfactory to continue the trials. One reason why there is a discrepancy between the analyses of model mice and the human trials is that as the pathogenesis of asthma in humans is heterogenous and diverse, it is important to cluster the asthma pa-

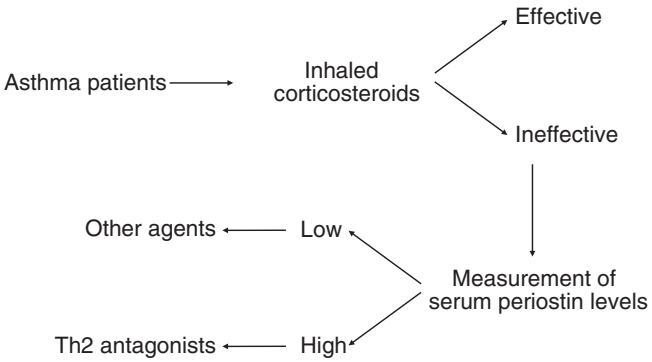


**Fig. 5** Novel algorithm for treatment of bronchial asthma patients. Inhaled corticosteroids (ICSs) are used as the first line of anti-asthma drugs. If the patients are resistant to ICSs, serum periostin levels are measured for these patients to evaluate whether these patients are Th2-high or Th2-low patients. Then if they show high serum periostin levels, which means that they are Th2-high asthma patients, Th2 antagonists such as lebrikizumab or omalizumab are recommended for them. If not, other agents or treatments are recommended.

tients based on their pathogenesis (endotypes) and to evaluate the efficacy of drugs in each endotype. For this reason, Genentech performed a phase IIa study of anti-IL-13 antibodies (lebrikizumab) for steroid-resistant asthma patients.[59] In this trial, lebrikizumab showed overall good efficacy in improving lung function for the patients. When the patients were divided into high and low periostin groups based on serum periostin levels, lebrikizumab showed significant efficacy for the high periostin group, whereas it had no efficacy for the low periostin group. Furthermore, clustering asthma patients into these groups was also useful for predicting the efficacy of anti-IgE antibodies (omalizumab).[60] From these findings, a novel algorithm for treatment of asthma patients is proposed as follows (Fig. 5): the first line of anti-asthma drugs is inhaled corticosteroids (ICSs). Although ICSs are effective for most patients, 5-10% are resistant to it.[61,62] By measuring serum periostin, the steroid resistant patients can be grouped into Th2-high and Th2-low patients. Then Th2 antagonists such as lebrikizumab or omalizumab are recommended for the Th2-high patients. This suggests that serum periostin can be a good biomarker to predict the efficacy of biologics for asthma. Diagnostics useful for prediction of efficacy of drugs are called "companion diagnostic". Periostin is the first example of companion diagnostics in the field of allergic diseases.

We also evaluated the usefulness of measurement of serum periostin to treat asthma patients with ICSs.[63,64] The high serum periostin group is characterized as asthma patients with late-onset, eosinophil-dominant, and aspirin-intolerant asthma. We showed that the high serum periostin group tended to be insensitive to ICS or to have a risk of exacerbation after tapering ICS doses. Matsumoto *et al.* describe the usefulness of periostin in bronchial asthma in the same issue of this journal.[65] Taken together, these findings show that periostin is a useful biomarker to develop stratified medicine for bronchial asthma.

## PERIOSTIN AS A PROMISING MOLECULAR TARGET FOR DEVELOPING THERAPEUTIC AGENTS AGAINST ALLERGIC DISEASES

As periostin plays an important role in the pathogenesis of allergic diseases, it is a promising molecular target for developing therapeutic agents against these diseases. As we mentioned earlier, we showed that periostin is critical for exacerbation and persistence of allergic skin inflammation in model mice.[4] In this study, we evaluated the effects of neutralizing antibodies against $\alpha_v$ integrin, a functional receptor for periostin, and applied these antibodies to two models: preventive and therapeutic. In the preventive model, when anti-$\alpha_v$ integrin antibodies are administered together with allergens, AD-like phenotypes induced by antigens are almost completely diminished. In the therapeutic model, even when anti-$\alpha_v$ integrin antibodies are administered after AD-like phenotypes induced by antigens are established, AD-like phenotypes were decreased. These results indicate a possibility that blocking a vicious circle including periostin and $\alpha_v$ integrin reversibly improves allergic skin inflammation, which demonstrates that periostin is a promising molecular target for developing therapeutic agents against these diseases.

There are two strategies to develop antagonists against periostin (Fig. 6). The first strategy is to

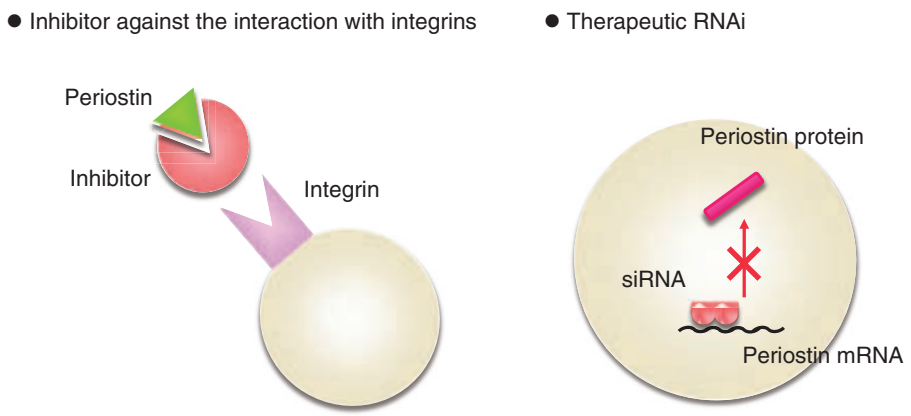


**Fig. 6** Strategies to develop antagonists against periostin. One strategy to develop antagonists against periostin is to search for a molecule to block the interaction between periostin and it receptors, integrin molecules (left panel). A second strategy is to search for a molecule to down-regulate the periostin expression (right panel).

search a molecule to block the interaction between periostin and its receptor, $\alpha_v$ integrin. The second is to search for a molecule to down-regulate periostin expression. Anti-periostin neutralizing antibodies aiming to block the interaction between periostin and $\alpha_v$ integrin have been developed.[66] It has been assumed that the YH sequence in the second FAS1 domain is the binding site for integrins, which may explain the ability of periostin to associate with integrin molecules in spite of its lack of the RGD sequence. These antibodies have shown therapeutic effects in a mouse model of pulmonary fibrosis[67] and bronchial asthma (Bentley *et al*. American Thoracic Society International Conference 2013). It is surprising that systemic administration of the antibodies improves the pathogenic phenotypes in spite of abundant expression of periostin in the whole bodies. An RNA interference (RNAi) method has been applied to down-regulate the periostin expression and has had beneficial effects on proliferative diabetic retinopathy[45] and progression of cancer cells.[68,69] Although this strategy involves problems in drug delivery, it is attractive in that antagonists based on RNAi are sure to be cheaper than biologics.

## PERSPECTIVES

Increasing evidence has shown the significance of periostin as a novel mediator in allergic inflammation. Periostin has a unique function as an inflammatory mediator linking immune cells and resident cells in inflamed lesions. Furthermore, advances have been made in applying periostin to development of novel diagnostics and therapeutic agents for allergic diseases. Both the concept of a molecular mechanism in which periostin is involved and the clinical application targeting periostin in allergic inflammation can be extended to other inflammatory diseases, malignancies, and developmental biology because periostin acts as a remodeling molecule in a wide variety of healthy and pathologic states.

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