Roles of Periostin in Respiratory Disorders

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Abstract

Periostin is a matricellular protein that has been implicated in many disease states. It interacts with multiple signaling cascades to modulate the expression of downstream genes that regulate cellular interactions within the extracellular matrix. This review focuses on the role of periostin in respiratory diseases, including asthma and idiopathic pulmonary fibrosis, and its potential to help guide treatment or assess prognosis. Epithelial injury is a common feature of many respiratory diseases, resulting in the secretion, among others, of periostin, which is subsequently involved in airway remodeling and other aspects of pulmonary pathophysiology. In asthma, periostin is recognized as a biomarker of type 2 inflammation; *POSTN* gene expression is up-regulated in bronchial epithelial cells by IL-13 and IL-4. Serum periostin has been evaluated for the identification of patients with increased clinical benefit from treatment with anti-IL-13 (lebrikizumab, tralokinumab) and anti-IgE (omalizumab) therapy and may be prognostic for increased risk of asthma exacerbations and progressive lung function decline. Furthermore, in asthma, periostin may regulate subepithelial fibrosis and mucus production and may serve as a systemic biomarker of eosinophilic airway inflammation. Periostin is also highly expressed in the lungs of patients with idiopathic pulmonary fibrosis, and its serum levels may predict clinical progression. Overall, periostin contributes to multiple pathogenic processes

across respiratory diseases, and peripheral blood levels of periostin may have utility as a biomarker of treatment response and disease progression.

Keywords: periostin; biomarker; asthma; idiopathic pulmonary fibrosis; airway remodeling

At a Glance Commentary

Scientific Knowledge on the Subject: The matricellular protein periostin has an overarching role in tissue remodeling and repair across respiratory diseases. Periostin is recognized as a biomarker of type 2 inflammation in asthma and has been implicated in the pathogenesis of idiopathic pulmonary fibrosis.

What This Study Adds to the Field: This review describes the contribution of periostin to multiple pathogenic processes in respiratory disease and discusses its potential as a biomarker of treatment response and disease progression in asthma and idiopathic pulmonary fibrosis. Further research is needed to explore the potential utility of periostin for clinical decision making.

Periostin is a matricellular protein initially isolated from a mouse osteoblast cell line (1). Matricellular proteins are nonstructural extracellular matrix (ECM) proteins that are highly expressed at sites of injury or

inflammation. There, they bind to growth factors and cytokines and modulate their activity, while interacting with other ECM proteins to mediate tissue remodeling (2). Expression of *POSTN*, the gene that

encodes human periostin, can be induced by transforming growth factor (TGF)- β , IL-4, and IL-13 (3, 4). The periostin molecule is composed of a cysteine-rich domain within the N-terminal region,

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four fasciclin I domains, and an alternative splicing domain within the C-terminal region. Up to nine splice variants have been identified, including the full-length transcript that encodes an ~90-kD secreted protein and includes all exons (5). Although the functional significance of the different splice variants is not fully understood, they could potentially be important in different tissues and diseases (6).

Periostin interacts with multiple signaling cascades to modulate the expression of several genes, such as collagen, chemokines, and TGF- β (6, 7). Periostin is highly expressed in the periosteum and in the periodontal ligament, and primarily overexpression (rather than underexpression) of periostin is observed in stromal cells associated with various malignancies, including non-small cell lung carcinoma, breast cancer, ovarian cancer, and thymoma. In addition, periostin plays a key role in cardiovascular development and in remodeling after myocardial injury (6). Table 1 attempts to provide an overview of other disease states involving periostin.

Periostin is also up-regulated in lung tissue in the context of several respiratory diseases, where it modulates pulmonary inflammation and remodeling; however, its precise functions in the lung have not been fully elucidated. This review draws on the collective experience of the authors in this field, focusing on the role of periostin in asthma and idiopathic pulmonary fibrosis (IPF) and discussing its potential utility as a biomarker in predicting disease progression or response to treatment.

Table 1. Elevated Periostin Expression Is Associated with Multiple Disease States

Bronchial asthma (55, 56)
Atopic dermatitis (57, 58)
IgG4-related sclerosing sialadenitis (59)
Eosinophilic otitis media (60)
Allergic rhinitis and chronic rhinosinusitis (14)
Chronic rhinosinusitis with nasal polyps (13, 14)
Eosinophilic esophagitis (24)
Idiopathic pulmonary fibrosis (39)
Drug-induced pulmonary fibrosis (20)
Scleroderma (61)
Proliferative diabetic retinopathy (62)
Bone marrow fibrosis (63)
Cancer (64, 65)
Cardiovascular disease (66)
Nonalcoholic fatty liver disease (67)
Preeclampsia (68)
Lupus nephritis (69)

This is not an exhaustive list.

Periostin in Airway Development and Pulmonary Epithelial Repair

Dynamic periostin is pivotal in airway development and epithelial repair processes during development in both health and disease. For example, periostin expression is initially down-regulated in the lungs of mice exposed to hyperoxic conditions during the alveolar period of lung development (8), followed by subsequent up-regulation during the TGF- β -mediated fibrotic response (8, 9), and is up-regulated in infants with bronchopulmonary dysplasia (9). During neonatal alveolar septation, the 80-kD fibrillar isoform level remains constant, but levels of the 84-kD fibrillar and 90-kD secreted isoforms are robustly up-regulated during secondary septal morphogenesis (8). Furthermore, neonatal periostin-null mice are initially resistant to hypoxia exposure at birth (8) but are subsequently protected from alveolar simplification after later hyperoxic pulmonary injury (9). Biphasic expression of periostin correlates with the presence of α -smooth muscle actin-positive myofibroblasts, which are required for early alveolar septation in the developing murine lung (8). Finally, periostin is differentially expressed in airway epithelial cells (AECs) from children with asthma compared with cells from atopic children without asthma and healthy children, supporting the hypothesis that *POSTN* is associated with subepithelial remodeling in asthma, even in the growing lung (10). Further research in this area is needed to elucidate roles of periostin during lung development and its potential involvement in the pathogenesis of asthma.

The more general role and mechanisms of action of periostin in epithelial repair is less clear. In an *in vitro* scratch wound model, recombinant human periostin enhanced wound repair in AECs as a soluble factor but did not affect AEC migration as a substrate component (11), despite reports from an earlier study using the same cell line that demonstrated exogenous overexpression of periostin enhanced AEC proliferation and migration in culture (12).

Periostin in Disorders of the Upper Respiratory Tract

Periostin has been implicated during tissue fibrosis and remodeling in the nasal mucosa in a number of otolaryngologic diseases.

Periostin expression is up-regulated in allergic rhinitis, chronic rhinosinusitis (CRS) with nasal polyps (13), and aspirin-intolerant asthma (14). In addition, higher serum periostin levels were associated with increased severity of CRS in patients with aspirin-exacerbated respiratory disease (15). Further studies are warranted to elucidate the precise function of periostin in the pathogenesis of these diseases.

Periostin in Disorders of the Lower Respiratory Tract

Epithelial injury and damage are common biological processes in respiratory disease and can result from exposure to various stimuli such as environmental allergens or infections (6, 10). Bronchial and alveolar epithelial cell synthesis of factors such as periostin, TGF- β_2 , and vascular endothelial growth factor contribute to airway remodeling and other aspects of respiratory disease pathophysiology (Figure 1) (10, 16). The cell-specific actions of periostin are shown in Figure 2. Inflammatory cells (lymphocytes, neutrophils, and macrophages) release cytokines such as IL-4 and IL-13, which activate eosinophils to produce periostin (17). Subsequent periostin binding to α M β 2 and α 4 β 1 integrins on eosinophils leads to eosinophil localization, adhesion, and recruitment to airways (13, 18, 19). After an inflammatory stimulus, periostin released from epithelial airway cells has autocrine effects that include activation of TGF- β and up-regulation of type I collagen, and paracrine effects, which include TGF- β -mediated increases in type I collagen production in fibroblasts. In addition, periostin can increase the elastic modulus of gels formed by type I collagen, which could change the biomechanical properties of the airway. Periostin acts on fibroblasts, activating nuclear factor- κ B together with inflammatory cytokines such as tumor necrosis factor- α or IL-1 α followed by induction of inflammatory chemokines (20). Periostin induces differentiation of fibroblasts to myofibroblasts and enhances fibrosis by binding to other ECM proteins, such as collagen I, fibronectin, and tenascin-C, and by inducing collagen fibrillogenesis and cross-linking (21).

Periostin may influence epithelial remodeling by promoting epithelial-mesenchymal transition (21), in which

Figure 1. Secretion of periostin in the airway in response to IL-13 and proposed actions in asthma and idiopathic pulmonary fibrosis (IPF). Th2 = T-helper cell type 2.

AECs lose their epithelial properties and take on properties of mesenchymal cells that contribute to fibrosis (22). In addition, basal secretion of periostin by epithelial cells can lead to changes in the underlying matrix by altering collagen deposition and cross-linking of collagen fibrils (21).

Periostin has been associated with multiple respiratory disorders. Emerging evidence suggests elevated expression of periostin in the airways of a subset of patients with chronic obstructive pulmonary disease; further investigation is needed in this area (23). However, most studies to date have focused on the role of periostin in asthma and IPF and suggest that up-regulated periostin plays an integral role in the pathogenesis of these disorders (3, 21, 24–27). This will be discussed in more detail in the following paragraphs.

Periostin in Asthma

The heterogeneity of asthma is an important aspect of the disease and is increasingly recognized as a crucial factor in guiding treatment. Several asthma phenotypes have been proposed, each with distinct features and the potential for differential responses

to treatment (28). Asthma phenotypes have been defined according to clinical and physiologic parameters, such as disease severity, response to treatment, frequency of exacerbations, or the presence of chronic airflow obstruction. Another way to describe phenotypes is based on their relationship to intrinsic triggers, such as aspirin or other antiinflammatory drugs or extrinsic irritants (e.g., pollutants or environmental allergens). Additional phenotypes have been identified on the basis of the predominant inflammatory cell type involved; eosinophilic or noneosinophilic inflammation can be recognized using invasive methods or direct airway sampling (bronchial biopsies or induced sputum) or by measuring noninvasive biomarkers (29). When the shared phenotypic characteristics in a subset of asthma are due to a common underlying mechanism driving disease pathophysiology, the asthma subset may be termed an “endotype” (28).

One common endotype of asthma is characterized by a type 2 inflammatory process that is perpetuated by the activity of type 2 cytokines. These include IL-4, IL-5, and IL-13, each of which can contribute to the pathogenesis of asthma (28). IL-13

directly contributes to many of the hallmarks of asthma pathophysiology, including mucus production, IgE class switching, subepithelial fibrosis, and airway hyperresponsiveness. IL-4 primarily promotes T-helper 2 cell differentiation and IgE class-switching, whereas IL-5 promotes eosinophilopoiesis, eosinophil maturation, and survival (30, 31).

POSTN, together with *CLCA1* and *serpinB2*, is among the most highly differentially expressed genes in the bronchial epithelium of patients with asthma (27), and *POSTN* alone or as part of a three-gene signature can be used to distinguish patients with asthma into type 2–high or type 2–low subtypes (32). These two phenotypes differ significantly in the levels of IL-13 and IL-5 detected in bronchial biopsies and in clinical characteristics such as airway hyperresponsiveness, blood and airway eosinophilia, and subepithelial fibrosis (32). Therefore, noninvasive biomarkers that reflect type 2–high and type 2–low asthma subtypes would be extremely valuable (32). IL-13 and IL-4 can both stimulate the secretion of periostin from lung fibroblasts (3), and IL-13–stimulated epithelial cells

Figure 2. Pleiotropic effects of periostin. Inflammatory cells (lymphocytes, neutrophils, and macrophages) release cytokines to induce periostin secretion from stromal cells. Periostin binds to eosinophils, mediating eosinophil localization, adhesion, and recruitment to airways. After an inflammatory stimulus, periostin derived from epithelial airway cells activates transforming growth factor (TGF)- β and up-regulates type I collagen. Periostin acts on fibroblasts, activating nuclear factor- κ B and promoting the expression of inflammatory cytokines and chemokines. Periostin induces differentiation of fibroblasts to myofibroblasts. By binding to other extracellular matrix (ECM) proteins and inducing collagen fibrillogenesis and cross-linking, periostin enhances fibrosis.

have been shown to secrete large quantities of periostin from their basolateral aspect (21). Thus, periostin is a candidate systemic biomarker of IL-13 and IL-4 activity. In response to *in vitro* stimulation with IL-13, activated AECs secrete periostin into the underlying matrix, where it exerts autocrine and paracrine effects. Periostin induces activation of the TGF- β signaling pathway and increases collagen deposition and gel elasticity, thereby contributing to airway remodeling and potentially changing the biomechanical properties of the airway (21). Evidence has suggested that collagen deposition in the subepithelial basement membrane in bronchial asthma may be

type 2 cytokine dependent (3). A small, preliminary study has reported that periostin deposition in the airway subepithelium of patients with asthma, which was associated with decline in FEV₁ over 20 years, may correlate with collagen I deposition. Although IL-4 and IL-13 were not measured in this study, it was suggested that CD8 T lymphocytes indirectly up-regulated periostin levels via increased production of type 2 cytokines (33). This preliminary research requires further investigation to determine the relationship between periostin and type 2 inflammation as well as other asthma phenotypes. The availability of “omics”

techniques (transcriptomic, proteomic, lipidomic, and metabolomic) will allow us to identify multidimensional phenotypes of severe asthma and new treatment targets, which will help further understanding of any potential relationships (34).

Several studies have also investigated the clinical implications of high systemic periostin levels in patients with asthma. In one study, high serum periostin concentrations were correlated with specific disease characteristics, including older age at onset of asthma, higher blood eosinophil counts, and lower pulmonary function (35). In addition, high periostin levels are

associated with a higher prevalence of concomitant nasal disorders such as aspirin-intolerant asthma and CRS with nasal polyps (15, 35).

The precise role of periostin in airway function is still unclear; however, periostin appears to contribute to several pathogenic processes in asthma, including subepithelial fibrosis, eosinophil recruitment, and mucus production from goblet cells. Subepithelial accumulation of periostin also promotes adhesion and motility of type 2-conditioned eosinophils and may serve as a guide for eosinophil migration in the ECM in asthmatic airways (18). Given the potential role of periostin in eosinophil accumulation (24), it has been studied as a systemic biomarker for eosinophilic airway inflammation in asthma (36, 37). Using a logistic regression model, including fractional exhaled nitric oxide (Fe_{NO}), serum IgE, and blood eosinophils (other putative biomarkers of type 2 airway inflammation), high periostin was the best single predictor of airway eosinophilia in patients with severe asthma that was uncontrolled despite maximal inhaled corticosteroid (ICS) treatment ($P = 0.007$) (36). Periostin also had the least inpatient variability across three visits when compared with Fe_{NO} and blood eosinophils (36).

Two studies performed using periostin-deficient mice suggest that periostin may have protective effects in the setting of allergen challenge. Both studies showed that periostin-deficient mice have increased airway hyperresponsiveness to methacholine after ovalbumin sensitization and challenge (26) or after challenge with *Aspergillus fumigatus* antigen (25). In one of these studies, periostin-deficient mice also had less mucus metaplasia (26), but in the other they did not (25). Neither study found that periostin deficiency altered the inflammatory cell populations in the lung after allergen challenge, but both reports suggested modest increases in peripheral inflammation with periostin deficiency (e.g., increased peripheral T-cell cytokine production and serum IgE) (25, 26). These two studies appear to stand in contrast to another study that identified a specific defect in allergen-induced eosinophil recruitment to the lungs in periostin-deficient mice (24) as well as a study demonstrating that periostin is required for house dust mite-induced allergic airway disease in mice (38). These findings

parallel the human data, which support a pathogenic role for periostin in human asthma contributing to type 2 inflammation in the lung rather than restraining it.

Periostin in IPF

Periostin has been linked to IPF, the most common condition among a heterogeneous group of respiratory diseases of unknown etiology, collectively known as idiopathic interstitial pneumonias (IIP) (39). IPF is a chronic and ultimately fatal disease in which excessive deposition of ECM proteins and distortion of pulmonary architecture progressively lead to respiratory failure (20).

Preclinical evidence supporting a role for periostin in lung fibrosis comes from studies using a mouse model in which periostin expression has been shown to coincide with the appearance of fibrosis (20, 40). Periostin-deficient mice are protected from fibrosis after bleomycin injury (20, 40), which is suggested to result from impaired production of chemokines by periostin-deficient fibroblasts in mice on a BALB/c background (20). In C57Bl/6 mice, periostin may be important for the postinflammatory fibroproliferative phase of bleomycin-induced fibrosis, whereas inflammatory responses are similar between periostin knockout mice and wild-type littermates (40).

Periostin is highly expressed in the lungs and detected in the circulation of patients with IPF (39, 40). It localizes to areas of active fibrosis, fibrotic foci, and subepithelial and subendothelial regions in IPF lungs, and plasma levels of periostin at baseline predict clinical progression at 48 weeks in patients with IPF (40). Serum periostin levels in IPF are significantly higher than those in healthy individuals or patients with other IIPs and are inversely correlated with pulmonary function in patients with IPF; these findings suggest periostin is a component of fibrosis in IIP and could potentially be used as a biomarker to distinguish histopathologic types of IIP (39). TGF- β and IL-13 are fibrogenic cytokines that are highly expressed in IPF lung tissue, and both may contribute to elevated periostin expression levels in fibrotic lung parenchyma (41, 42). Similar to asthma, alternative splicing of the *POSTN* gene has been detected in IPF lung samples,

and specific splice variants may be involved in IPF pathogenesis (43).

Cross-linking between collagen fibrils, catalyzed by lysyl oxidases, determines the mechanical properties of connective tissues. Periostin can activate bone morphogenetic protein-1 to cleave lysyl oxidase, promoting its activation on the ECM and increasing collagen cross-linking (44). The resultant stiffening of the matrix is believed to promote fibroblast activation, which may perpetuate the progressive nature of IPF. Indeed, OC-20, an antibody that blocks periostin and integrin interactions, limited fibrotic progression and improved survival in the bleomycin mouse model (40).

Periostin as a Biomarker in Respiratory Disorders

Periostin as a Predictive Biomarker of Response to Treatment in Asthma

Corticosteroids are the mainstay of asthma treatment and provide adequate control in the majority of patients. However, around 5 to 10% of patients have severe asthma that is uncontrolled despite the use of inhaled corticosteroids (ICS) and requires more intensive therapy. Although several new biologic therapies are likely to become available in the near future, not all patients will benefit equally from these treatments; therefore, there is a need to identify and validate biomarkers that can be used to predict response to a targeted therapy.

Based on the accumulated data linking periostin expression to type 2 inflammation in asthma (21, 27, 32), its potential as a clinically validated biomarker to predict the response to treatments targeting type 2 cytokines is being investigated.

Several monoclonal antibodies against IL-13 are being evaluated in clinical trials as treatments for type 2 asthma. Lebrikizumab is an IgG4 humanized monoclonal antibody that specifically binds to IL-13 and prevents IL-13-induced heterodimerization of the IL-4R α /IL-13R α 1 receptor complex (45). In a study of mild allergic asthma, patients with higher baseline levels of periostin showed a greater reduction in late asthmatic response after lebrikizumab treatment compared with patients with lower levels of periostin at baseline (46). Compared with other biomarkers, including IgE, blood eosinophil count,

and an IgE/blood eosinophil composite, periostin showed the greatest predictive value in identifying patients who received clinically meaningful benefit from lebrikizumab treatment (46). In a subsequent study of moderate-to-severe asthma (MILLY; NCT00930163), patients with higher baseline levels of serum periostin showed greater improvements in lung function than those with lower levels. Lebrikizumab treatment led to significantly improved FEV₁ from baseline in those with serum periostin greater than or equal to 50 ng/ml but exhibited minimal clinically meaningful benefit in patients with serum periostin less than 50 ng/ml (47). This finding was replicated in two pooled phase IIb studies (LUTE and VERSE; NCT01545440, NCT01545453) in patients with uncontrolled asthma despite receiving ICS plus a second controller. Here, lebrikizumab treatment also resulted in a reduction in the severe exacerbation rate by 60% in patients with periostin levels greater than or equal to 50 ng/ml (48). By contrast, in a dose-ranging study of lebrikizumab in patients with asthma not taking ICS (MOLLY; NCT00971035), lebrikizumab treatment did not result in a statistically significant change in FEV₁, and the effects were similar by periostin subgroup (49). However, in MOLLY, there was an imbalance in periostin-high and periostin-low patients in the placebo-treated patient group, which may have contributed to uncertainty of the estimates in that study.

Periostin levels were also measured in a phase IIb trial of the anti-IL-13 antibody tralokinumab in patients with severe asthma. In this study, there was a trend toward reduced exacerbation rates with tralokinumab in the subgroup with high periostin levels (50). This improvement was not statistically significant, although this may be due to the small sample size (n = 150).

Finally, there is evidence from an analysis of one clinical study, the results of which need confirmation in additional studies, that periostin is a predictive biomarker of response to omalizumab (Xolair), a recombinant humanized monoclonal antibody that selectively binds to free IgE (51). In the omalizumab EXTRA study, there was a trend toward a decreased rate of severe exacerbations (by 30%) in patients

with uncontrolled severe asthma after omalizumab treatment in the periostin-high subgroup (those with a serum periostin level $\geq$ 50 ng/ml), versus only 3% in the serum periostin-low group (those with serum periostin < 50 ng/ml) (51).

Periostin as a Prognostic Biomarker

Prognostic biomarkers could potentially be used in asthma and other respiratory diseases to predict the risk of poor disease control, thereby allowing treatment optimization. Several studies have investigated the prognostic value of periostin in asthma and other respiratory diseases. In one preliminary study in which 20 patients with asthma were followed up for 20 years, the amount of periostin deposition and the numbers of cells positive for osteopontin (another ECM protein) in the bronchial subepithelium were associated with a long-term decline in FEV₁ (33). In a multicenter cohort study of 224 patients with asthma receiving ICS, polymorphisms in the *POSTN* gene were related to higher serum periostin levels and a decline in FEV₁ of greater than or equal to 30 ml per year (52). Among several serum biomarkers, including high-sensitivity C-reactive protein and eosinophil cationic protein, periostin was the only marker associated with an accelerated decline in FEV₁ ($\geq$ 30 ml/yr): high serum periostin levels were significantly correlated with a greater annual decline in FEV₁ ($P = 0.02$) (52). Furthermore, in a *post hoc* cluster analysis, the association between serum periostin and a decline in FEV₁, despite ICS therapy, was found to be most evident in the cluster characterized by patients with late-onset asthma and severe eosinophilic inflammation (53). Taken together, these findings suggest that serum periostin has potential to be clinically validated for use as a prognostic biomarker to predict the risk of lung function decline, particularly in patients with late-onset and eosinophil-dominant asthma. The results of a substudy of the aforementioned cohort trial suggested high serum periostin could also be used as an additional biomarker to improve the identification of ICS-insensitive patients among those with elevated FE_{NO}, whereas ICS-insensitive patients are defined as those with an accelerated

decline in FEV₁ or a risk of asthma exacerbations despite receiving high-dose ICS treatment (54).

A prognostic relationship between periostin and risk of asthma exacerbations has also been observed in clinical studies. In the omalizumab EXTRA study, in which subjects were required to have had experienced at least one exacerbation in the previous year, severe exacerbation rates over 48 weeks in the placebo arm were 0.93 and 0.72, respectively, in the periostin-high and periostin-low subgroups (51). The severe exacerbation rate per year in the LUTE and VERSE lebrikizumab studies was also higher in placebo-treated patients with high serum periostin levels than in periostin-low patients (1.01 vs. 0.48, respectively) (48). Conversely, in the phase II study of lebrikizumab in patients with moderate-to-severe asthma, the rate of severe exacerbations through Week 24 in the placebo group of the intent-to-treat population was 0.25 in the periostin-high subgroup, compared with 0.33 in the periostin-low subgroup; however, this study was not powered to detect an effect on exacerbations (47).

The prognostic value of periostin has also been investigated in IPF. In a multicenter, observational cohort study of 54 patients with IPF (COMET [Correlating Outcomes with Biochemical Markers to Estimate Time Progression in Idiopathic Pulmonary Fibrosis]; NCT01071707), plasma periostin levels predicted clinical disease progression at 48 weeks, suggesting that measures of periostin could also be used as a prognostic biomarker to enable stratification of patients for clinical trials in IPF (40). This finding is consistent with the results of another study in which periostin levels in patients with IPF were inversely correlated with pulmonary function (39).

Conclusions

Periostin has demonstrated roles in several clinical studies, as discussed above, as a predictive biomarker (of response to treatment) and a prognostic biomarker (of disease worsening) in respiratory disease, particularly asthma. Periostin is a biomarker of type 2 inflammation in asthma, and ongoing clinical trials seek its clinical validation as a biomarker to identify patients

likely to receive clinical benefit from anti-IL-13 treatment. Periostin may also contribute to asthma pathobiology, including subepithelial fibrosis, airway hyperresponsiveness, eosinophil recruitment, and mucus production, and thus be a modulator of disease progression. In IPF, periostin is believed to be involved in lung fibrosis and was

predictive of clinical progression in certain clinical studies, as discussed above. More research is needed to fully elucidate the roles of periostin in the pathophysiology of respiratory diseases such as asthma and IPF and to fully understand its utility for clinical decision making. It is evident that periostin will continue to be an

important focus of respiratory research in the future. ■

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