



Periostin, a novel biomarker of T_H2-driven asthma

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Purpose of review

Asthma is a heterogeneous disease with multiple, overlapping phenotypes. Biomarkers are currently being investigated to better characterize the disease phenotypes and to identify the responders to specific targeted therapies. This review focuses on the emerging data surrounding the use of one such biomarker for T helper 2 (T_H2)-driven asthma: periostin.

Recent findings

Periostin is an extracellular matrix protein that is induced by interleukin (IL)-4 and IL-13 in airway epithelial cells and lung fibroblasts. It has proven to be an important biomarker of T_H2-associated airway inflammation and a potential predictor of airway eosinophilia. It has also been shown to predict response to treatment with inhaled corticosteroids in patients with these characteristics. Furthermore, recent asthma clinical trials have established that serum periostin may have value in predicting the response to targeted therapy with biologic agents such as lebrikizumab and omalizumab.

Summary

Emerging data suggest a role for periostin in refining asthma phenotypes and predicting the response to targeted therapy. Although early data are promising, further investigations are needed to confirm these findings and to identify other clinical applications in which periostin may be valuable.

Keywords

asthma, periostin, T_H2 inflammation

INTRODUCTION

Asthma is a chronic lung disease affecting over 300 million people worldwide [1]. This disease is characterized by chronic airway inflammation, airway hyperresponsiveness, mucus hypersecretion, sub-epithelial fibrosis, and variable degrees of airflow obstruction [2]. Although asthma was initially thought of as a single disease, extensive data have shown significant heterogeneity in the disease phenotypes and endotypes, with different responses to treatment [3–8,9^{*}]. This understanding has led some to suggest abandoning the use of asthma as a specific disease concept, as it may be more of a syndrome that describes multiple underlying distinct diseases [10].

It is this heterogeneity of asthma that has resulted in an increased interest in using biomarkers to better individualize therapeutic approaches to the disease. Utilization of biomarkers has become so commonplace in clinical research and clinical practice that the U.S. National Institutes of Health convened a Health Biomarkers Definitions Working Group to assess the use of biomarkers in clinical trials and develop consensus terminology [11]. A biomarker has been defined as ‘a characteristic that is objectively measured and evaluated as an

indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention’. An ideal biomarker should have the following characteristics [12–15]:

- (1) a clear relationship with the disease pathophysiology;
- (2) reliability and reproducibility;
- (3) changes in response to treatment;
- (4) simple detection quantification;
- (5) low cost;
- (6) high sensitivity, specificity, and positive and negative predictive values.

Recent data suggest that 50% of patients with asthma demonstrate a T helper 2 (T_H2)-driven phenotype [16]. Coinciding with the better phenotypic

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KEY POINTS

- Asthma is a heterogeneous disease with multiple phenotypes and endotypes.
- Biomarkers can aid in the phenotypic characterization of asthma and in predicting the response to treatment.
- Periostin is a valuable evolving biomarker of T_H2-associated airway inflammation.
- Periostin has shown promise in research studies in predicting the response to treatment with inhaled corticosteroids, lebrikizumab, and omalizumab.
- Future research needs to identify the potential utility and feasibility of periostin in the clinical setting.

characterization of asthma, serum periostin has garnered substantial interest as a potential biomarker in T_H2-induced airway inflammation. In this review, we highlight the scientific discoveries that led to the utilization of periostin as a biomarker in asthma and detail some of the promising data from recent clinical trials using it as a biomarker.

T_H2-DRIVEN AIRWAY INFLAMMATION IN ASTHMA

Asthma has long been considered as T_H2-driven inflammatory disease that is linked with atopy, allergy, eosinophilic inflammation, and corticosteroid responsiveness. More recent phenotypic data from cluster analyses support the idea that much, but not all, of asthma is T_H2 driven [5,6]. The T_H2 immune response is associated with early-onset (atopic or allergic) asthma, later-onset (eosinophilic) asthma, and exercise-induced asthma [9[¶]]. In the current understanding of T_H2-driven airway inflammation, inhaled allergen triggers the activation of mast cells and subsequent release of leukotrienes and prostaglandins in the early asthmatic response [17,18[¶]]. The late response is characterized by the release of interleukin (IL)-4, IL-5, IL-13, and eotaxin by activated T_H2 cells with subsequent IgE isotype switching, eosinophil activation, and smooth muscle cell proliferation [19,20]. IL-25 and IL-33 are also secreted by airway epithelial cells, leading to the activation of dendritic cells and release of IL-5 and IL-13 from innate lymphoid cells [17,18[¶],21,22]. IL-13 in the allergic airway has been implicated in macrophage activation [23], eosinophil recruitment and activation [24,25], mucus hypersecretion [20,26], production of inducible nitric oxide synthase [27], and transformation of fibroblasts into myofibroblasts with resulting collagen deposition [20]. Additionally, IL-13 has been shown to induce airway hyperresponsiveness

through direct effects on cells within the airway [26,28]. The immune processes involved in T_H2-associated airway inflammation are highlighted in Fig. 1. Although these processes may not be present in all asthma phenotypes, this pathway does lend itself to targeted therapy and the potential use of biomarkers to predict responders to a specific therapy or gauge subsequent treatment response.

PERIOSTIN IN ALLERGIC AIRWAY INFLAMMATION

Periostin (encoded by *POSTN*) is a secreted, 90-kDa extracellular protein with structural homology to the adhesion molecule fasciclin I (FAS I) that was originally detected in osteoblasts [35], but is also known to be expressed in mesenchymal cells in other organs [36–38]. Microarray studies of gene expression in the airway epithelium of asthmatic patients have shown a greater than four-fold increase in *POSTN* compared with healthy controls [29], making periostin among the most highly expressed genes in asthma. Periostin in human bronchial epithelial cells [29–31] and lung fibroblasts [32] is inducible by IL-4 and IL-13. Although periostin was assumed to be an adhesion molecule, it was work by Takayama *et al.* [32] which demonstrated that periostin had the ability to bind fibronectin, tenascin-c, collagen V, as well as to colocalize with other extracellular matrix proteins involved in subepithelial fibrosis.

Periostin, secreted by the airway epithelial cells in response to stimulation by IL-4 and IL-13, has been shown to have downstream effects of mediating collagen synthesis [33] and fibrillogenesis [33,34] by binding collagen [34] and activating transforming growth factor beta (TGF-β) [33]. In a well designed study, Sidhu *et al.* [33] demonstrated that periostin, secreted basally by the airway epithelial cells in response to IL-13, has autocrine effects on epithelial cell function, including activation of TGF-β and upregulation of collagen as well as TGF-β-mediated activation of fibroblasts.

Interestingly, work on periostin-deficient mice yielded mixed results [39–41]. Blanchard *et al.* [39] administered intranasal *Aspergillus fumigatus* antigen to wild-type and periostin-deficient mice, and subsequently performed bronchoalveolar lavage. Bronchoalveolar lavage fluid (BALF) in the periostin-deficient mice showed a statistically significant decrease in eosinophil numbers, suggesting that periostin may facilitate eosinophilic inflammation in the lung [39]. Gordon *et al.* [40] similarly performed *A. fumigatus* antigen challenge on wild-type and periostin-deficient mice, but found differing results. They were able to show that *Aspergillus* antigen challenge in wild-type mice resulted in an

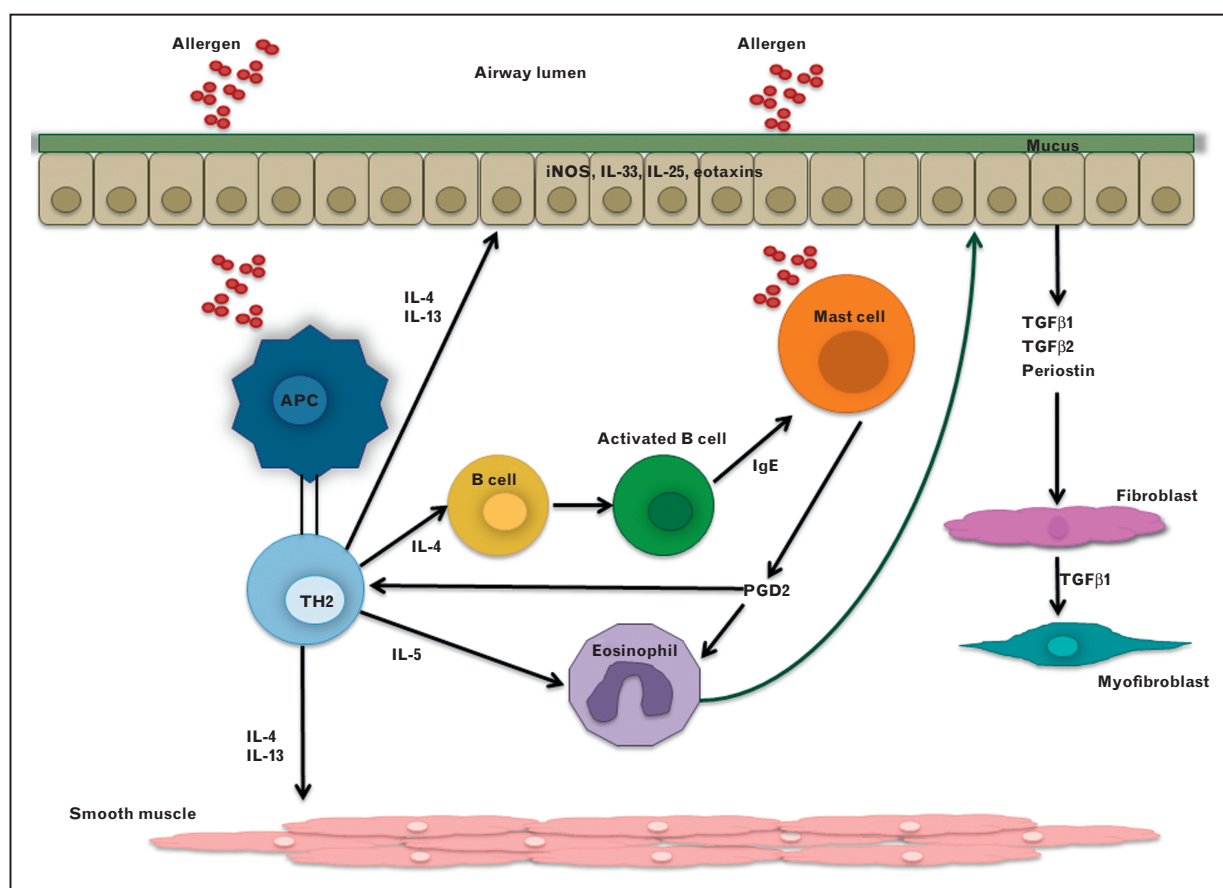


FIGURE 1. T_H2 immune processes occurring in the airways of asthmatic patients [9[■],17,18[■],19–23,25,26,29–34]. IL, interleukin; iNOS, inducible nitric oxide synthase; TGF, transforming growth factor; T_H2 , T helper 2.

increase in periostin in the subepithelial space [40], consistent with the prior findings of immunolocalization in human airway epithelial cells [33]. Perhaps surprisingly, compared with wild-type controls, periostin-deficient mice developed increased airway hyperresponsiveness and serum IgE levels following allergen challenge without differences in mucus metaplasia and peribronchial fibrosis [40]. These changes were associated with a decrease in TGF- β 1 and Foxp3 gene expression in periostin-deficient mice, suggesting the possibility of a protective role for periostin through TGF- β -induced T regulatory cell differentiation [40].

A subsequent study by Sehra *et al.* [41] also suggested a protective role for periostin. In an ovalbumin-induced model of sensitization, the authors demonstrated that periostin-deficient mice had no difference in eosinophils, IL-4, IL-5, or interferon- γ in BALF when compared to wild-type controls [41]. However, they did demonstrate an increase in airway hyperresponsiveness and significantly enhanced mucus production by goblet cells with a concomitant increase in expression of *Gob5* and *Muc5ac* in the periostin-deficient mice [41]. Finally,

a recent study in periostin-deficient mice suggested that periostin may be a critical mediator of amplification and persistence of allergic inflammation in a mouse model of skin inflammation, again suggesting a role for periostin in chronic T_H2 inflammation [42[■]]. Unfortunately, the conflicting results of these animal studies have made it difficult to fully understand the precise role of periostin in allergic airway inflammation.

PERIOSTIN AS A BIOMARKER

The importance of periostin as a biomarker for T_H2 inflammation was initially highlighted in a study by Woodruff *et al.* [29]. The authors used gene-expression microarrays to demonstrate that *POSTN*, along with *SERPINB2* and *CLCA1*, was upregulated in the airway epithelial cells of asthmatic patients. Baseline expression of *POSTN*, *SERPINB2*, and *CLCA1* was associated with good clinical response to corticosteroids, and treatment with corticosteroids led to the downregulation of these three genes [29]. The same group of investigators subsequently used this three-gene signature to identify T_H2 -high and T_H2 -low phenotypes in asthmatics and validated

their findings with bronchial biopsy specimens [16]. A significant improvement in forced expiratory volume in 1 s (FEV₁) was seen in patients receiving inhaled corticosteroids (ICS) in the T_H2-high but not the T_H2-low group [16]. Using a qPCR-based assay instead of microarray to determine the three-gene mean of *POSTN*, *SERPINE2*, and *CLCA1* yielded similar results [43]. The three-gene mean obtained by qPCR from the airway epithelial brushings of asthmatics identified T_H2 high and low populations, correlated with other T_H2 biomarkers [fractional exhaled nitric oxide (F_ENO), blood eosinophils, and provocative concentration of methacholine causing a 20% drop in FEV₁ (PC20)], and predicted FEV₁ improvement with ICS [43].

Other convincing data have contributed to the interest in using periostin as a biomarker in asthma. A study by Jia *et al.* [44^{***}] identified serum periostin as a systemic biomarker of airway eosinophilia in severe, uncontrolled asthmatics. Peripheral blood and induced sputum were collected and bronchoscopy was performed on severe, uncontrolled asthmatics (Asthma Control Questionnaire score >1.50, FEV₁ 40–80%) taking maximal ICS (>1000 µg/day fluticasone dipropionate or equivalent). In a logistic regression model, serum periostin was the single best predictor of sputum and tissue eosinophilia, showing superiority to blood eosinophils, IgE, and F_ENO. Importantly, serum periostin did not correlate with sputum or tissue neutrophilia [44^{***}]. These findings further support the role of periostin as a biomarker in T_H2 or eosinophilic inflammation.

More recently, a study by Kanemitsu *et al.* [45^{***}] contributed to the growing evidence that elevated serum periostin may help identify T_H2-mediated airway inflammation in asthmatics. Two hundred and twenty-four asthmatic patients treated with ICS for at least 4 years were enrolled in this observational study. Clinical indices, serum periostin levels, periostin gene polymorphisms from blood, and annual changes in FEV₁ were examined. High serum periostin levels (≥95 ng/ml) were associated with a decline in FEV₁ of at least 30 ml per year. Multivariate analysis found high serum periostin levels to be an independent predictor of decline in FEV₁. Supporting the previous work by Jia *et al.* [44^{***}], serum periostin levels were significantly higher in patients taking high-dose ICS (>1000 µg daily), suggesting that serum periostin may be a biomarker of eosinophilic airway inflammation that is at least partly refractory to ICS [45^{***}].

THE USE OF PERIOSTIN AS A BIOMARKER IN CLINICAL TRIALS

Periostin has also demonstrated value as a biomarker in predicting the response to T_H2 targeted therapy

with lebrikizumab, a humanized monoclonal antibody that binds and inhibits IL-13 [46]. Corren *et al.* [46] performed a randomized, double-blind, placebo-controlled study of lebrikizumab in 219 adults with uncontrolled asthma despite treatment with ICS. Lebrikizumab treatment was associated with a more pronounced effect on lung function in patients with high pretreatment levels of serum periostin. FEV₁ increased by 8.2% in the high-periostin treatment subgroup versus placebo compared with a 1.6% improvement in the low-periostin treatment subgroup compared to placebo. In a subsequent dose-ranging study evaluating the effect of lebrikizumab on FEV₁ in asthmatics not receiving ICS, periostin levels were not predictive of treatment response [47^{*}]. There were significant limitations that preclude drawing strong conclusions about the predictive value of periostin in this study. Limitations included insufficient power to detect differences between the periostin-high and periostin-low groups, a low number of placebo treated patients in the periostin-low group, and an imbalance in the periostin-high and periostin-low groups that was likely related to the periostin assay not being ready for use at the trial initiation. Despite these shortcomings, the findings suggest that IL-13 may not be the primary driver of lung function in asthmatics not taking ICS.

The ability of periostin to predict treatment response in T_H2-driven asthma has not been limited to ICS and lebrikizumab. Hanania *et al.* [48] performed a post hoc analysis of data from the EXTRA study to explore the potential of T_H2 inflammatory biomarkers in predicting therapeutic benefit with omalizumab treatment [49^{***}]. In this study of uncontrolled, severe persistent allergic asthmatics, exacerbation rate decreased by 30% in the high serum periostin group (≥50 ng/ml) compared with 3% in the low serum periostin group (<50 ng/ml) following treatment with omalizumab. Although promising, these results should be interpreted with caution given some of the limitations associated with a post-hoc analysis; however, these findings add to the accumulating data supporting periostin's ability to predict treatment response in T_H2-driven asthma.

FUTURE DIRECTIONS

Despite the mounting evidence supporting a potential role for periostin as a biomarker in T_H2-driven inflammation, much work remains to better clarify the potential utility of periostin in both clinical research and clinical practice. Future investigation should examine serum periostin in diseases that are characterized by T_H2 or eosinophilic inflammation, including asthma, atopic dermatitis, nasal

polyposis, and eosinophilic esophagitis. Further study is needed to better delineate how utilizing serum periostin can further refine specific asthma phenotypes. Cut-off values for high and low serum periostin levels still need to be established and validated. Additionally, further investigation is needed to determine the potential value of following serum periostin levels as a marker of response to specific asthma therapies. Until these matters are further clarified, the use of periostin as a biomarker will remain largely investigational.

CONCLUSION

The evolving data surrounding the heterogeneity of asthma and its associated phenotypes has made the development and utilization of biomarkers of utmost importance. Although the recently convened Asthma Outcomes Workshop highlighted multiallergen screening to determine atopy as the only core measure for future clinical trials, the importance of using supplemental biomarkers was also highlighted [50]. Mounting evidence supports the emergence of periostin as a potentially valuable biomarker for T_H2 -driven airway inflammation. Periostin, independently or in combination with other more conventional biomarkers, such as blood and sputum eosinophils, F_{ENO} , and IgE, has the potential to better refine current asthma phenotypes. Furthermore, periostin also holds promise in predicting responders to new or existing biological T_H2 -directed therapies for the treatment of asthma. Biomarkers, such as periostin, should continue to be utilized as surrogate endpoints in future asthma clinical trials. Yet, despite these advances, use of periostin alone or in combination with other biomarkers needs further study to better delineate its utility in characterizing asthmatic patients by phenotype and predicting their response to new or existing treatments.

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Conflicts of interest

There are no conflicts of interest.

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