Serum Periostin Level Interpretation in Asthmatic Children

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Abstract

Background: Asthma is a major public health problem that affects nearly 350 million people worldwide. It is also the most common chronic disease in childhood and adolescence. Several asthma phenotypes and endotypes have been identified. While 80% of children with asthma have allergies. In recent years, studies on the role of periostin in asthma have been published. Periostin is a cell matrix protein that was first identified in mouse periodontal ligament. It is secreted by bronchial fibroblasts and epithelial cells, acts as an immunomodulator, repairs connective tissue, and is involved in fibrogenesis. Significant periostin expression has been noted in the bronchial epithelial cells of children with asthma.

Keywords: Periostin, Bronchial Asthma

Bronchial asthma in Children:

Definition
A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or early morning.

Etiology
Factors that can contribute to asthma or airway hyperreactivity may include any of the following:

- Environmental allergens (e.g., house dust mites; animal allergens, especially cat and dog; cockroach allergens; and fungi)
- Viral respiratory tract infections
- Exercise, hyperventilation
- Gastroesophageal reflux disease
- Chronic sinusitis or rhinitis
- Aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, sulfite sensitivity
- Use of beta-adrenergic receptor blockers (including ophthalmic preparations)
- Obesity (1).
- Environmental pollutants, tobacco smoke
- Occupational exposure
- Irritants (e.g., household sprays, paint fumes)
- Various high- and low-molecular-weight compounds (e.g., insects, plants, latex, gums, wood dust, and fluxes; associated with occupational asthma)
- Emotional factors or stress
- Perinatal factors (prematurity and increased maternal age; maternal smoking and prenatal exposure to tobacco smoke; breastfeeding has not been definitely shown to be protective)
Pathophysiology:

The 2007 Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program (NAEPP) noted several key changes in the understanding of the pathophysiology of asthma.

The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses.

- Of the environmental factors, allergic reactions remain important. Evidence also suggests a key and expanding role for viral respiratory infections in these processes.
- The onset of asthma for most patients begins early in life, with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.
- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease severity.

The pathophysiology of asthma is complex and involves the following components:

- Airway inflammation
- Intermittent airflow obstruction
- Bronchial hyperresponsiveness

**Airway inflammation:**

The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. Varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present.

Antigen presentation by the dendritic cell with the lymphocyte and cytokine response leading to airway inflammation and asthma symptoms.

Some of the principal cells identified in airway inflammation include mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes. T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Other constituent airway cells, such as fibroblasts, endothelial cells, and epithelial cells, contribute to the chronicity of the disease. Other factors, such as adhesion molecules (eg, selectins, integrins), are critical in directing the inflammatory changes in the airway. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodeling of the airway.

The presence of airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The mechanisms involved include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells such as mast cells or nonmyelinated sensory neurons. The degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma.

A study by Balzar et al reported changes in airway resident mast cell populations from a large group of subjects with asthma and normal control subjects.

A greater proportion of chymase-positive mast cells in the airways and increased prostaglandin D2 levels were identified as important predictors of severe asthma as compared with other steroid-treated subjects with asthma.

Chronic inflammation of the airways is associated with increased bronchial hyperresponsiveness, which leads to bronchospasm and typical symptoms of wheezing, shortness of breath, and
coughing after exposure to allergens, environmental irritants, viruses, cold air, or exercise. In some patients with chronic asthma, airflow limitation may be only partially reversible because of airway remodeling (hypertrophy and hyperplasia of smooth muscle, angiogenesis, and subepithelial fibrosis) that occurs with chronic untreated disease. Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and IFN-α, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation. A study by Gauvreau et al found that IL-13 has a role in allergen-induced airway responses (5).

The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in westernized countries (6). This hypothesis is based on the concept that the immune system of the newborn is skewed toward Th2 cytokine generation (mediators of allergic inflammation). Following birth, environmental stimuli such as infections activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. However, unequivocal support for the "hygiene hypothesis" has not been demonstrated (7).

**Airflow obstruction:**
Airflow obstruction can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling. Acute bronchoconstriction is the consequence of immunoglobulin E-dependent mediator release upon exposure to aeroallergens and is the primary component of the early asthmatic response. Airway edema occurs 6-24 hours following an allergen challenge and is referred to as the late asthmatic response. Chronic mucous plug formation consists of an exudate of serum proteins and cell debris that may take weeks to resolve. Airway remodeling is associated with structural changes due to long-standing inflammation and may profoundly affect the extent of reversibility of airway obstruction (8).

Airway obstruction causes increased resistance to airflow and decreased expiratory flow rates. These changes lead to a decreased ability to expel air and may result in hyperinflation. The resulting overdistension helps maintain airway patency, thereby improving expiratory flow; however, it also alters pulmonary mechanics and increases the work of breathing.

**Bronchial hyperresponsiveness:**
Hyperinflation compensates for the airflow obstruction, but this compensation is limited when the tidal volume approaches the volume of the pulmonary dead space; the result is alveolar hypoventilation. Uneven changes in airflow resistance, the resulting uneven distribution of air, and alterations in circulation from increased intra-alveolar pressure due to hyperinflation all lead to ventilation-perfusion mismatch. Vasoconstriction due to alveolar hypoxia also contributes to this mismatch. Vasoconstriction is also considered an adaptive response to ventilation/perfusion mismatch.
Functions of Periostin in Asthma

Several trials to clarify the significance of periostin in the pathogenesis of asthma have been carried out using asthma model mice; however, the results are controversial and the conclusion remains uncertain. It was initially reported that when periostin deficient mice were challenged with ovalbumin or Aspergillus, airway hyper responsiveness (AHR), type 2 inflammation, and mucus production were also enhanced in these mice (9).

These results suggested that periostin protects against allergic inflammation in these model mice. In contrast, Bentley et al. reported that all of these features AHR, type 2 inflammation, and mucus production—were impaired in house dust mite (HDM)-challenged periostin deficient mice and by administration of neutralizing anti-periostin antibodies (10). These results suggested that, in contrast to the initial studies, periostin accelerates allergic inflammation in these model mice. They showed the importance of periostin in dendritic cells (DCs) in this context as adoptive transfer of HDM-treated bone marrow-derived DCs from wild-type mice into periostin-deficient mice restored HDM-induced asthma-like phenotypes. The reason for this contradiction is not yet known.

Kanemitsu et al., (11) examined the importance of Periostin deposition in asthma patients. They analyzed the correlation between Periostin expression in some biopsy samples that they took from asthma patients more than 20 years ago and recent changes of pulmonary function in those same patients. They found that deposition of Periostin in the bronchial sub epithelium in the samples was strongly inversely correlated with decline of ΔFEV1. These results support the notion that Periostin plays a role in accelerating airway allergic inflammation in asthma patients. We have examined the importance of Periostin as a matricellular protein in the process of inflammation using in vitro systems. We have shown that particularly the involvement of Periostin in the epithelial/mesenchymal interaction would be important for the pathogenesis of allergic diseases, including asthma (Fig. 7.3). In the three-dimensional organotypic co-culture system mimicking the epithelial/mesenchymal interaction in skin tissues, we showed that Periostin derived from fibroblasts stimulated by IL-13 acts on keratinocytes by itself activating NF-κB inducing production of pro inflammatory cytokines including TSLP (12).

Using the same system, Izuhara et al., (13) also showed that Periostin acts on fibroblasts together with IL-1α activating NF-κB inducing IL-6 (14). Moreover, Izuhara et al., (13) found that cooperative actions of Periostin and either TNF-α or IL-1α activate NF-κB in lung fibroblasts, followed by production of MCP1/3, CXCL1/2, and IL-1β, pro-inflammatory cytokines important for recruiting neutrophils and macrophages (15).

These results point to the capability of Periostin to activate NF-κB in tissue-resident cells such as epithelial cells and fibroblasts by itself or by cross talk with other pro-inflammatory mediators. Regarding Periostin actions on immune cells, it has been reported that it can act on eosinophils, inducing adhesion, super oxide generation, and TGF-β production (16). Thus, it is assumed that Periostin plays various roles as a pro-inflammatory mediator acting on both tissue-resident cells and immune cells.

Periostin as a Biomarker for Asthma:

A Biomarker for Type 2 (Th2-High) Asthma: It is now recognized that asthma is not a single disease but a syndrome (17). We have empirically classified asthma patients based on clinical features such as age of onset (pediatric vs. adult), IgE dependency (atopic vs. nonatopic), and responsiveness to inhaled corticosteroids (ICSs, steroid-responsive vs. steroid-resistant). These classifications are based on
phenotypes. In contrast, the significance of classifications based on molecular mechanisms of diseases, called endotypes, has recently emerged. Classifying asthma by type 2 vs. non-type 2 (or Th2-high vs. Th2-low) is an example of using endotypes (17).

This concept, “stratification of asthma patients,” is the basis for applying molecularly targeted drugs for asthma, as we will discuss later. The proportion of type 2 asthma defined by high expression of IL-5 and IL-13, signature type 2 cytokines, is estimated to be 50–70% of total asthma patients (18).

Asano and his colleagues have recently estimated the proportion of type 2 in severe asthma patients to be ~80% in a Japanese population. Fahy and his colleagues searched for biomarkers for type 2 asthma, finding that Periostin is highly expressed in bronchial tissues of type 2 asthma patients together with chloride channel regulator 1 (CLCA1) and serpin peptidase inhibitor, clade B, member 2 (SERPINB2) (19).

They then found that serum Periostin is high in type 2 asthma correlated with airway eosinophilia, compared to the fraction of exhaled nitric oxide (FeNO), peripheral blood eosinophils, YKL-40, and IgE levels (18). These results demonstrate that Periostin has emerged as a novel biomarker for type 2 asthma.

Our collaborators have intensively examined the characteristics of asthma patients correlated with serum Periostin levels, using Periostin ELISA kits with high sensitivity that we developed compared to other kits (20).

**A Biomarker for ICS Resistance:**

our collaborators have shown that Periostin is a component of the thickened basement membranes of asthma and is correlated with poor long-term prognosis (11), suggesting that Periostin has another characteristic as a biomarker for asthma reflecting remodeling or fibrosis. Matsumoto and her colleagues have demonstrated that Periostin is associated with resistance to ICSs, the first-line drugs for asthma patients.

In the KiHAC study, when they divided asthma patients into rapid decliners and non-rapid decliners, defined by patients with treatments by ICS showing a decline in FEV1 of more than or less than 30 mL/year, respectively, serum Periostin was higher in rapid decliners than in non-rapid decliners. This suggests that serum Periostin is associated with hypo responsiveness to ICSs in asthma (11).

When they clustered these patients based on their peripheral eosinophil and neutrophil numbers, cluster 3, which was characterized by high eosinophils and low neutrophil numbers and late onset, showed that the difference in decline of FEV1 between the Periostin-high and Periostin low groups was more significant compared to the overall patients. This suggests that in this cluster, serum Periostin is more associated with poor responsiveness to ICSs (21).

The association of serum Periostin with poor responsiveness to ICSs was also observed in other studies (20).

**Nagasaki et al. (21)** showed more direct evidence for this association; when they tapered ICS treatment, asthma reflected of type 2 inflammation and remodeling/fibrosis resistance to ICSs prediction of efficacy of molecularly targeted drugs for asthma, particularly IL-4/IL-13 antagonists.

Characteristics of Periostin as a biomarker for asthma K. Izuhara et al. 77 patients with high Periostin showed a higher risk for instability than those with low Periostin.

Introducing ICS to asthma patients promptly decreased FeNO levels, whereas it sustained high serum Periostin levels. This finding suggests that ICS improves superficial inflammation consistent with decreased FeNO secreted from epithelial cells, whereas ICS does not improve the
inflammation of deep layers consistent with sustained serum Periostin. Such limited efficacy of ICSs for asthma patients may lead to resistance to ICSs in Periostin-high asthma patients showing high remodeling or fibrosis.

**A Biomarker for Predicting the Efficacy of Molecularly Targeted Drugs for Type 2 Asthma:**
Currently, many drugs for type 2 asthma targeting IgE, IL-4/IL-13 (receptor), IL-5 (receptor), TSLP, CCR3, CCR4, CCL11, and CRTH2 are being developed. Some of them, two kinds of anti-IL-5 antibodies mepolizumab and reslizumab—are already available at the start of 2018 (13).

Since periostin is a surrogate biomarker for type 2 asthma, particularly a downstream molecule of IL-4 and IL-13, several trials to apply periostin to a biomarker to predict efficacy of asthma drugs targeting IL-4 and IL-13 have been performed. The first trial was carried out in the phase IIb study for lebrikizumab, an antiIL-13 antibody, developed by Roche/Genentech (23).

They demonstrated that when they set the cutoff value of serum periostin at 50 ng/mL, the high periostin group showed good responsiveness to lebrikizumab, whereas the low periostin group showed poor responsiveness to it, demonstrating that serum periostin is a very useful biomarker to predict the efficacy of lebrikizumab. However, in the phase III study, lebrikizumab did not show enough efficacy for asthma patients, and development was ended (23).

In the phase IIb study of tralokinumab, another anti-IL-13 antibody, developed by AstraZeneca/MedImmune, both periostin and DPP-4, another type 2 biomarker, showed good ability to discriminate between good and poor responders to it as well as to lebrikizumab (24). SanofiRegeneron has developed dupilumab, an anti-IL-4 receptor α chain antibody that inhibits both IL-4 and IL-13 signals, as the first molecularly targeted drug for atopic dermatitis (24).

They have also developed dupilumab as an anti-asthma drug. In the phase IIb study, they used the blood eosinophil number as a biomarker to stratify patients; however, although the high eosinophil group tended to respond better than the low eosinophil group, dupilumab showed statistically significant efficacy in both groups (17).

Izuhara et al., (13) examined the ability of serum periostin for this purpose instead of blood eosinophil number using the same samples as a post hoc study, finding that serum periostin showed a good ability to discriminate between good and poor responders as defined by improved lung functions (unpublished data, presented at the ERS Congress, 2016). Taken together, serum Periostin has the potential to be a useful biomarker to predict the efficacy of IL-4/IL-13 antagonists.

The usefulness of periostin as a biomarker to predict of efficacy of molecularly targeted drugs for type 2 asthma was examined for omalizumab, an anti-IgE antibody, provided by Novartis/Genentech. At this point, two studies have shown its usefulness (23).

To our knowledge, these are the only studies so far to examine the usefulness of serum periostin as a biomarker to predict efficacy of molecularly targeted drugs for type 2 asthma except IL-4/IL-13 antagonists. These results point to the possibility that serum periostin is useful to predict efficacy of more molecularly targeted drugs for type 2 asthma other than IL-4/IL-13 antagonists.

**ConflictofInterest:** No conflict of interest.

**References**


