

Serum periostin as a marker of T_H2-dependent eosinophilic airway inflammation

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The symptoms of asthma in a majority of patients can be fairly well controlled with modest doses of inhaled corticosteroids¹ or a combination of inhaled corticosteroids and long-acting bronchodilators.² A small proportion of patients, estimated to be approximately 5% to 10% of all asthmatic patients, require very high doses of inhaled or ingested corticosteroids for asthma control. The reason for their relative steroid insensitivity might be multifactorial, varying from molecular mechanisms of glucocorticoid receptor kinetics,³ pharmacogenomics,⁴ a predominantly neutrophilic bronchitis,⁵ and airway smooth muscle responsiveness to steroids and bronchodilators.⁶ The development of biomarkers that accurately identify the precise mechanism would be extremely useful for drug development to target the underlying pathophysiologic abnormality in these patients.

The presence of eosinophils in the airway lumen, as identified based on quantitative sputum cell counts, is one of the predictors of response to corticosteroids.⁷ The persistence of eosinophils in sputum despite high doses of corticosteroids is also a biomarker to select patients for treatment directed at T_H2 cytokines, such as IL-5, which is involved in eosinophil maturation and differentiation.^{8,9} However, access to a laboratory and perceived difficulties in collecting and processing sputum might limit the widespread access and utility of this biomarker.

Jia et al¹⁰ report that levels of periostin, a matricellular protein that is partly regulated by IL-13,¹¹ measured in serum might be a simple alternative to identify airway eosinophilia and therefore response to treatment directed at the T_H2 pathway, specifically against IL-13.¹² This conclusion was reached by demonstrating increased serum periostin levels in patients with airway luminal and tissue eosinophilia despite high doses of inhaled or ingested corticosteroids, correlations with blood and sputum eosinophilia, modest sensitivity and specificity using receiver operating characteristic curves, and repeatability over a 5-week observational period. Serum periostin measurements were more discriminatory than blood eosinophil, fraction of exhaled nitric oxide, and YKL-40 measurements to detect airway eosinophilia.

Although these results are encouraging, one needs to be cautious about interpreting them and any extension of this interpretation to clinical practice. Although the airway epithelium can indeed be stimulated by IL-13 and IL-4 to secrete periostin,¹¹ this protein is not specific to asthma or the airway epithelium. Periostin is a secreted protein that shares structural homology to the axon guidance protein FAS1 in insects and was originally named *Osf2*.¹³ Periostin is particularly highly homologous to β ig-h3, which promotes cell adhesion and spreading of fibroblasts¹³ and epithelial¹⁴ and ovarian cells¹⁵ and the development of cardiac valves.¹⁶ It is therefore not surprising that this protein has been demonstrated to be increased in patients with a number of conditions associated with increased cell division, cell turnover, invasion, and angiogenesis. Therefore periostin is increasingly recognized as a marker to predict the behavior of a number of cancers,¹⁷ such as colon, pancreas, bladder, thyroid, breast, lung, and gall bladder cancers, and other conditions associated with cellular hyperplasia and fibroblast proliferation that occur in pulmonary¹⁸ and renal fibrosis,¹⁹ pulmonary hypertension, and dermatitis. The protein is also expressed in the epithelium of the gastrointestinal tract in patients with eosinophilic gastroenteritis,²⁰ and this might be a reflection of the upregulated IL-13 activity seen in patients with this condition.

Although there is no dispute that periostin promotes eosinophilic inflammation in response to T_H2 cytokines,²¹ the precise role of periostin in asthmatic patients is still unresolved. It has also been reported to protect against allergen-induced hyperresponsiveness.²² Overall, our current understanding of periostin is that it is upregulated in adult tissues under a number of diverse adverse conditions, including tissue injury, stress, or both, that might not always be dependent on a T_H2 immune response.

However, this should not deter clinicians from using this biomarker to direct anti-T_H2 therapies in patients with eosinophilic asthma if there is convincing evidence that this protein is specific for airway eosinophilia and that patients with high levels of periostin respond favorably to such therapies. Although an arbitrary level of 25 ng/mL had a positive predictive value of 93% and a negative predictive value of 37% for sputum ($\geq 3\%$) or tissue ($\geq 22/\text{mm}^2$) eosinophilia to identify an "eosinophilic phenotype," it is not currently known whether this is influenced by current dose of corticosteroids or by the severity of asthma. In other words, the changes in periostin levels or its responsiveness have not been evaluated with an increase or a downtitration of steroids in a placebo-controlled randomized trial. The measurement properties of serum periostin are not known in other conditions associated with eosinophilic bronchitis, such as nonasthmatic cough, chronic hyperplastic rhinosinusitis, or smoker's bronchitis, that might be associated with eosinophilic bronchitis. Finally, the treatment effects of an anti-IL-13 mAb in those patients with high periostin levels were modest and not sustained over the 23-week treatment period.¹²

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Although sputum eosinophil counts are an accurate reflection of a T_H2 -dominant mechanism in those asthmatic patients whose symptoms are uncontrolled on high doses of corticosteroids, a simple blood test to accurately predict response to treatment with biologic agents would be ideal and potentially clinically very useful. Periostin shows promise, particularly in patients with severe asthma, but it remains to be seen whether it will serve that purpose.

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