Review Article

Periostin – Its role in asthma and inflammation: A review

G. R. Sathya[1], Priscilla Johnson[2]*, Subhasis Das[1], B. Rajagopalan[3], D. Rekha[1]

ABSTRACT

Asthma is a diverse illness with many, overlying phenotypes. Biomarkers are currently being inspected and developed to distinguish the disease phenotypes and to categorize the responders to appropriate treatments. Recently, an extracellular matrix protein, namely Periostin, has been identified as a novel biomarker for asthma. Periostin production and release is facilitated by IL-4 and IL-13 in the epithelial cells of the airways and the fibroblasts in lungs. It has been established as a significant biomarker of Th2-mediated airway irritation as well as a diagnostic marker for eosinophilic airway diseases. It has also been on trial in attempts to predict the response in asthmatics who are on inhaled corticosteroids. However, additional inquiries are warranted to establish the exact role of Periostin in allergic airway disease. The articles for this review were collected using key words like 'asthma', 'Periostin', 'inhalational corticosteroids', 'Type 2 inflammation' making use of search engines like Google scholar, Medline, Pubmed. It is hoped that this review will aid the practitioners and asthmatics to understand the role of Periostin in detecting steroid hypo-responsive asthma.

KEY WORDS: Asthma, Periostin, Th2 Inflammation

INTRODUCTION

Asthma is designated as a "syndrome" rather than a disease. It is a chronic inflammatory condition of the airways which expresses complex immunological processes. Asthma is usually designated as a Type 2 (Th2) driven allergic disorder mediated by eosinophils, neutrophils, mast cells, and lymphocytes. However, various studies which were based on the phenotypic data suggested that the pathogenesis of asthma always cannot be contributed by the Th2 inflammatory response.[1] The atopic asthma with early onset, eosinophilic asthma with late onset, and exercise-induced asthma are prone to Th2 resistance. The mechanism of Th2 mediated immune response can be explained as follows: The initial response to the entry of an allergic substance in the airway is the activation of mast cell reaction followed by the release of leukotrienes and prostaglandins.[2,3] Following this, a late response, which is triggered by Th2 cells cause the release of interleukin IL-4,5,13 and eotaxin. These interleukins, in turn, are considered to be responsible for macrophage activation[4] eosinophil activation and enrolment,[5] mucus hypersecretion, and alteration of fibroblasts into myofibroblasts leading to subepithelial fibrosis.[6]

As the kind of inflammatory process is likely to cause corticosteroid resistance and hence affect treatment response, studies support the need for categorizing the various phenotypes of asthma based on the main inflammatory cells. With an idea to provide a better prognosis and quality of life to asthmatics, the search for newer reliable biomarkers was started. Keeping periostin as such novel biomarker in mind, the articles for this review were collected using keywords such as "asthma," "Periostin," "inhalational corticosteroids," and "Th 2 inflammation" using search engines such as Google Scholar, Medline, and PubMed. It is hoped that this review on periostin will aid the practitioners and asthmatics to recognize the clinical utility of periostin in detecting steroid hyporesponsive asthma and thereby would definitely pose a positive impact on the treatment modality and disease prognosis.

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

[1]Department of Physiology, Pondicherry Institute of Medical Sciences, Puducherry, India, [2]Department of Physiology, Sri Ramachandra Institute of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu, India, [3]Department of Chest and Tuberculosis, Sri Ramachandra Institute of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu, India

***Corresponding author:** Dr. Priscilla Johnson, Department of Physiology, Sri Ramachandra Institute of Higher Education and Research (Deemed to be University), Porur, Chennai-600116, Tamil Nadu, India. E-mail: priscillajohnson@sriramachandra@edu.in

Received on: 18-03-2019; Revised on: 21-05-2019; Accepted on: 26-05-2019

PERIOSTIN AS A BIOMARKER IN ASTHMATICS

Currently, biomarkers have been found to play a major role in designating the disease phenotypes and to categorize the responders to the exact mode of treatment among asthmatics. For a substance to be designated as a perfect biomarker, it is expected to fulfill the following attributes: (a) It should possess a definitive association with the disease pathophysiology, (b) should have an assured reliability and reproducibility, (c) should be quantitatively measurable, d) should show change in the levels following treatment, (e) should be simple and cost effective, and (f) should ensure increased specificity, sensitivity, positive, and negative predictive qualities.[6]

Periostin is an extracellular matrix (ECM) protein molecule categorized as belonging to the Fasciclin family due to its structural similarity with fasciclin 1 protein (FAS1), an axonal guidance protein recognized in insects, and Algal-CAM, big-h3, MBP-70, and Stabilin I and II – other mammalian proteins.[7,8] Periostin is also designated as osteoblast-particular factor 2 since it was first identified in the periosteum and periodontal ligament of mice.[9] This matricellular protein stimulates a cell and brings about the inflammatory process by attaching itself to the receptors and a few integrins-αVβ1, αVβ3, αVβ5, α6β4, and αMβ2 on the cell surface. It has recently emerged as a novel biomarker in asthmatics which identifies airway hyper-responsiveness due to its numerous exclusive features like its rapid and easy migration from the inflammatory site to the neighboring blood vessel, the basal acceptable concentration at which it can be detected as well as the availability of highly sensitive enzyme-linked immunosorbent assay (ELISA) kits possessing low detection limits.

Periostin- Source and Structure

An investigation by Nuzzo *et al*. has demonstrated the expression of periostin in fetal and adult tissues, including periodontal ligament, embryonic periosteum, adrenal gland, cardiovascular valve, lung, placenta, thyroid tissues, and periodontal ligament.[10] Fibroblasts also release periostin.

It has an N-terminal and a C-terminal domain. In the mid-portion between the two terminals, there are four tandemly arranged FAS1 domains. The N terminal domain is rich in cysteine molecule called as EMI (EMILIN) domain and the splicing domain is at the C-terminal end. To maintain the structural stability, periostin possesses the property to interact with other proteins like collagen I, fibronectin present in the EM whereas the FAS1 domains binds with bone morphogenetic protein and tenascin-C Figure 1.[11-13] These protein interactions are said to be responsible for the transforming growth factor-beta (TGF-β) mediated sub-epithelial fibrosis.[14]

Genetic Expression of Periostin

Gene expression of periostin is encoded as POSTN. Microarray research has shown a four-fold increased expression of POSTN gene in the airway epithelia of asthmatics as compared to controls, making periostin as the most commonly involved genetic factor in asthma. In humans, the genetic expression could have been contributed by IL 4 and 13.[15,16]

Periostin Preclinical Studies

Studies on periostin deficient mice have reflected varied consequences. Some investigators have demonstrated that periostin protects mice from allergic airway inflammation, while few other studies have demonstrated that periostin quickens allergen-induced eosinophil recruitment in the esophagus and lung,[7,11,12] thus exhibiting opposing outcomes in periostin deficient mice.

The study by Takayama *et al*. displayed that when a wild type mice were exposed to Aspergillus antigen content it caused an upsurge in periostin in the subepithelial region, which was similar to previous findings which demonstrated its presence in the

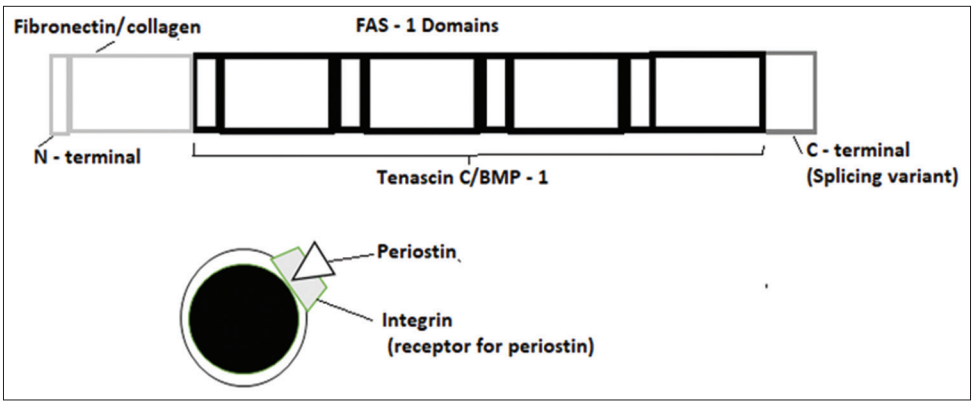

Figure 1: Structure of Periostin

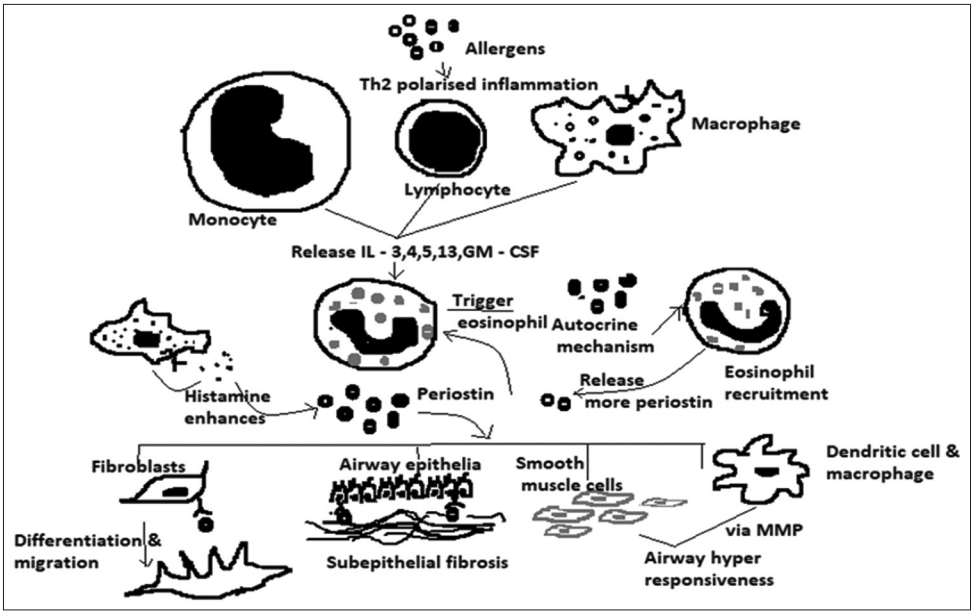

Figure 2: Role of periostin in the pathogenesis of asthma

epithelial cells of human airways.[14] The POSTN+/+ mice model which had raised expression of periostin levels in the inflammatory cells of peribronchial, and airway liquid lining layer has shown higher airway responsiveness.[13,17] Studies in POSTN +/+ mice model have also shown an elevated number of eosinophils and enhanced inflammatory airways as compared to periostin lacking mice.[18,19]

However, subsequent research suggested the defensive role of periostin. Following sensitization of mice deficient in periostin with ovalbumin, the study proved an upsurge of mucus production by goblet cells, which suggested a hyper-responsive airway. However, the authors established that bronchoalveolar lavage fluid (BALF) obtained from mice deficient in periostin did not show any change in the number of eosinophils, IL-4, IL-5, or interferon-gamma as compared with controls.[7] Another study by Blanchard *et al*.[12] have also shown that BALF from mice deficient in periostin exhibited a significant reduction in the number of eosinophils. A study by Wenzel *et al*.[20] further established the protective role of periostin. It showed that a reduction in TGF-β1 and Foxp3 gene in mice deficient in periostin was responsible for amplified Immunoglobulin E (IgE) levels and airway hyper-receptiveness.

Role of Periostin in the Pathogenesis and Steroid Resistance among Asthmatics

Asthma is considered as an inflammatory condition which is heterogeneous due to the involvement of various cellular components. The understanding of pathogenesis that underlies various inflammatory process in asthmatics becomes essential to clinically distinguish the asthma phenotypes and thereby to start the asthmatics on a focused therapeutic regimen at the molecular level.[8,20] There are few trials which have attempted to group asthmatics based on the presence of cells such as neutrophils and eosinophils and then have studied the pathogenesis that underlies each of those.[21,22] After obtaining baseline values from healthy subjects, asthmatics were categorized into four groups based on neutrophilic and eosinophilic presence. The four inflammatory subtypes included paucigranulocytic, neutrophilic, mixed granulocytic, and eosinophilic. Those studies have shown that in eosinophilic asthma, Th2 pathways were stimulated resulting in the release of cytokines such as IL-4,5,9 and 13.[8]

In the 1990s, investigations of model mice established the significance of Th 2 immunological response that underlies the pathogenesis of asthma.[23] From that point, the focus of investigations was to recognize which signature cytokine (IL- 4, IL-5, or IL-13) was vital for Th 2 immunity in asthma. Moreover, it turned out, that the presence of IL-13 alone was enough to cause asthma-like phenotypes in mice, while the blockage of IL-13 signals alone was sufficient to inhibit asthma-like phenotypes in mice model induced with ovalbumin.[24] Especially, IL-13 present in the epithelial cells of the airways has appeared to be responsible for inducing goblet cells and for improving airway hyperresponsiveness.[25,26]

All the above-mentioned studies have led to the identification of an evolving biomarker Periostin, a downstream molecule of IL-4,5,13 as, which has been hypothesized to play a significant role in the inflammatory process of eosinophilic asthma, thereby causing airway hyper-responsiveness.[18] Currently,

researchers are actively involved in exploring the role of periostin in mediating Th 2 inflammatory response in asthmatics. In humans, it is found that despite a high dose of inhaled corticosteroid (ICS), the upregulation of IL-4/13, is responsible for the prolonged ongoing of eosinophilic inflammation in the airways.[27-30]

Periostin levels in humans can be obtained from serum and BALF. Serum periostin levels are elevated only in a proportion of asthmatic patients on ICS[27] while other asthmatics were within the normal range. Studies have shown that periostin levels in serum or BALF can be considered as better markers for airway eosinophilia among asthmatics with Th 2 inflammatory response as compared to such indicators as the fraction of exhaled nitric oxide (FeNO), serum IgE levels or blood eosinophil count.[31,32] In most studies so far, the periostin levels have been estimated in serum and sputum of asthmatics without considering the inflammatory phenotype.[33] With the available information, it becomes essential to explain the inflammatory role of periostin in various asthma phenotypes.

Allergen exposure mediates Th2 inflammatory process which causes recruitment of IL-4,13 and TGF-β secreting immune cells. IL-3,5 or GM-CSF from immune cells can cause activation and recruitment of eosinophils which release periostin, thus produced, initiate a vicious cycle by following an autocrine mechanism through its receptors on eosinophils, epithelial cells, and fibroblasts. In addition, periostin induces migration of fibroblasts, its differentiation to myofibroblasts leading to ECM production by binding to other ECM proteins (e.g., tenascin-C, collagen I, and fibronectin) and by triggering fibrillogenesis of collagen.[9] Periostin released by macrophage can enhance the secretion of matrix metalloproteinases. Expression of periostin is enhanced by histamine.[9]

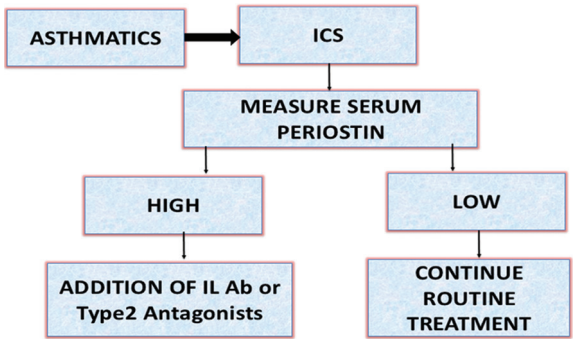

Figure 2: Proposed protocol for asthma management

Considering the role of periostin in the inflammatory process that underlies asthma, it appears to consider periostin as a suitable replacement biomarker to identify steroid hyporesponsiveness. With this view, a schematic protocol for asthma management can be proposed, as illustrated in Figure 2 and Table 1.

The initial line of antiasthma treatment is ICSs. However, in the near future, few new biologics, including anti-IL-13 and anti-IL-5, would be available as a therapeutic regimen for steroid-resistant asthmatics. Asthmatics whose symptoms remain uncontrolled with ICS can be considered as steroid-resistant and are expected to benefit by these biologics. In the measurement of serum periostin could be considered as a companion diagnostic so as to determine which patients would respond to these new biologics.[34]. If a patient demonstrates a high periostin level, Th 2 antagonist ought to be included. In case a patient demonstrates a low periostin level, other treatments or agents can be recommended.[23]

Furthermore, serum periostin levels may reflect chronic or latent inflammation and remodeling of the asthmatic airways with ICS action.[34] As compared to

Table 1: Levels of serum periostin in allergic inflammation

Author, Journal and Year	Disease	Method of Periostin assessment	Observation
Kim *et al*.[41]	AERD	ELISA	Serum periostin levels are significantly elevated in AERD patients and are associated with AERD phenotype and disease severity
Kou *et al*.[39]	AD	ELISA	There was a significantly elevated serum periostin in AD, and these levels showed a positive correlation with the severity of the disease
Qin *et al*.[42]	CRS	Immunohistochemistry	Reduced gene expression of periostin following resolution of disease suggests that POSTN may be represented as an indicator or biomarker in the pathogenesis of CRS and its responsiveness to treatment
Laury *et al*.[43]	AFRS	IF and semi-quantitative RT-PCR	Periostin levels show a positive correlation with the severity of radiological scores. Increased levels of periostin in AFRS can possibly indicate intense eosinophilic inflammation

AD: Atopic dermatitis, ELISA: Enzyme-linked immunosorbent assay, AFRS: Allergic fungal rhinosinusitis, CRS: Chronic rhinosinusitis, AERD: Aspirin exacerbated respiratory disease

FeNO and blood eosinophil counts, serum periostin levels are usually steady and exhibit minimal change with repeated trials, which is a desired characteristic of a dependable biomarker.

Serum Periostin in Childhood Asthma

In contrast with adult asthma, the value of periostin in childhood asthma is still under discussion.[35] Certain studies have demonstrated the minimal difference in the periostin levels between the control and patient group. Conversely, few studies[36] did not identify relationships of serum periostin levels among patients with childhood asthma and control subjects.[37] Few studies have shown high levels of serum periostin among childhood asthmatics until they reached adolescence. One explanation behind the conflicting outcomes with serum periostin levels in patients with childhood asthma could be an elevated baseline serum levels of periostin in children.[37]

Periostin in Inflammation

Under basal circumstances, various cell kinds such as epithelial cells, fibroblasts, and eosinophils express periostin.[38] However, based on the exposure, the type of development of inflammatory response due to periostin varies. For example, in mice exposed to house dust mite, induction of periostin created development of increased receptiveness in airways by acting on the airway epithelium, sub-epithelium, smooth muscle, and inflammatory cells, while in mice which received OC-20 (a neutralizing antibody to periostin) inoculation showed a shortened airway accessibility.[17] Furthermore, patients diagnosed with atopic dermatitis had high serum periostinas compared to those with psoriasis vulgaris and healthy subjects.[39] In addition, it was found that connection can be established between periostin and thymus and stages of activation regulated chemokine, levels of lactate dehydrogenase, and eosinophil counts, but cannot be correlated to IgE levels. Polymerase chain reaction as well as ELISA could be used to identify gene expression of periostin in the sputum of asthmatics. *In vitro* and *in vivo* assays have proved the raised levels of POSTN and TWIST1 in the fibroblast-like synoviocytes (FLSs) of rheumatoid arthritis patients (FLSs) and patients with skin irritation.[40]

CONCLUSION

Periostin, a multifunctional protein, is produced by a variety of immune cells. Increased expression of periostin and an upsurge of POSTN is linked to the presence of an ongoing inflammatory process involving Th2 immune response. Elevated periostin levels are found to be connected with refractory Th2 eosinophilic irritation and remodeling of the airways causing the decline of pulmonary function in asthmatics. Furthermore, due to its high sensitivity and specificity, it can be considered as an ideal biomarker that can be used as a companion diagnostic for categorizing and modifying the treatment modality among asthmatics.

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Source of support: Nil; Conflict of interest: None Declared