Allergology International. 2014;63:143-151
DOI: 10.2332/allergolint.13-RAI-0663

REVIEW ARTICLE

Review Series: Periostin: From Pathogenesis to Clinical Application in Allergic Diseases

Periostin in Allergic Inflammation

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ABSTRACT

Periostin, an extracellular matrix protein belonging to the fasciclin family, has been shown to play a critical role in the process of remodeling during tissue/organ development or repair. Periostin functions as a matricellular protein in cell activation by binding to their receptors on cell surface, thereby exerting its biological activities. After we found that periostin is a downstream molecule of interleukin (IL)-4 and IL-13, signature cytokines of type 2 immune responses, we showed that periostin is a component of subepithelial fibrosis in bronchial asthma, the first formal proof that periostin is involved in allergic inflammation. Subsequently, a great deal of evidence has accumulated demonstrating the significance of periostin in allergic inflammation. It is of note that in skin tissues, periostin is critical for amplification and persistence of allergic inflammation by communicating between fibroblasts and keratinocytes. Furthermore, periostin has been applied to development of novel diagnostics or therapeutic agents for allergic diseases. Serum periostin can reflect local production of periostin in inflamed lesions induced by Th2-type immune responses and also can predict the efficacy of Th2 antagonists against bronchial asthma. Blocking the interaction between periostin and its receptor, α_v integrin, or down-regulating the periostin expression shows improvement of periostin-induced inflammation in mouse models or in *in vitro* systems. It is hoped that diagnostics or therapeutic agents targeting periostin will be of practical use in the near future.

KEY WORDS

allergy, atopic dermatitis, bronchial asthma, inflammation, periostin

INTRODUCTION

A typical inflammatory response is composed of four stages: 1) invasion by microbes or damage of tissues; 2) sensing infection or tissue damage by the immune system; 3) production of mediators including cytokines, bioactive amines, and eicosanoids by the immune system; and 4) effects of the mediators on target tissues.[1] Once the invaded microbes are eliminated or the damaged tissues are repaired, the inflammatory responses are terminated. However, if the inflammatory response persists, a chronic inflammatory state will ensue. Chronic inflammatory responses often cause tissue changes including remodeling, fibrosis, and metaplasia, which lead not only to the decline or loss of normal tissue functions, but also to the onset of new clinical symptoms.[1]

Since allergic diseases such as bronchial asthma and atopic dermatitis (AD) triggered by allergen invasions usually become chronic, the affected lesions in patients with these diseases present histologically with chronic inflammation. Asthma patients show mucus metaplasia, smooth-muscle hypertrophy, and enhanced deposits of subepithelial matrix proteins, termed "airway remodeling".[2] These histological changes are thought to lead to the airflow limitations and airway hyper-responsiveness (AHR) found in these patients. In AD patients, epidermal changes are evident, including epidermal thickness called acanthosis and hyper-/parakeratosis.[3] Although the exact pathological role of acanthosis remains unclear, we speculate that it provides a basis for supplying massive proinflammatory mediators from keratinocytes.[4,5]

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Conflict of interest: KI received research funding from Shino-Test, Chugai Pharmaceutical, AQUA Therapeutics; honoraria as Scientific Advisor for Chugai Pharmaceutical, AQUA Therapeutics; and a patent fee from F. Hoffmann-La Roche. The rest of the authors have no conflict of interest.
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Received 22 November 2013.

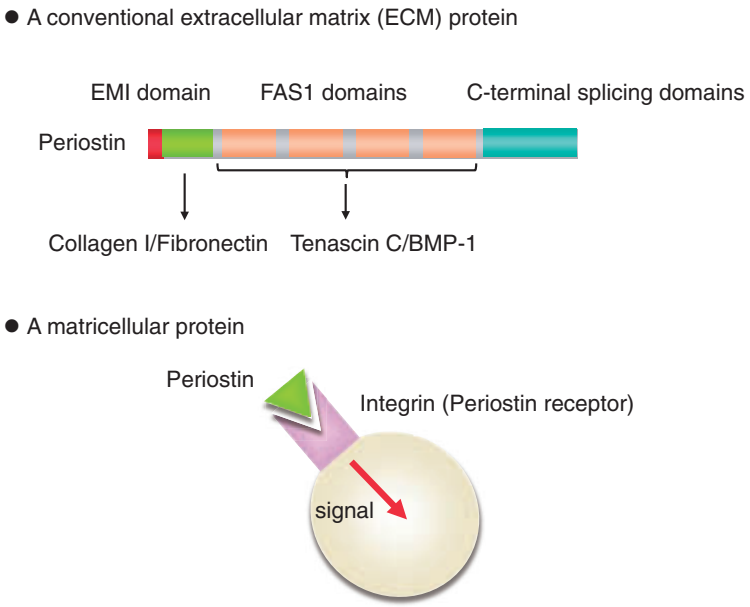

Fig. 1 Two faces of periostin. Periostin has two faces: a conventional ECM protein (upper panel) and a matricellular protein (lower panel). As a conventional ECM protein, periostin is important for maintaining tissue/organ structure or generating fibrosis, whereas it is important for cell activation as a matricellular protein. Periostin is composed of an EMI domain at the N terminus, four tandemly aligned FAS1 domains in the middle, and splicing domains at the C terminus. ECM proteins or a proteinase that can bind to the EMI domain or the FAS1 domains are depicted. In contrast, periostin binds to integrin molecules on cell surface transducing intracellular signals.

Periostin, an extracellular matrix (ECM) protein, has recently emerged as a novel mediator in chronic states of allergic diseases and plays an important role in tissue remodeling in allergic inflammation. In this review article, we focus on the significance and clinical application of periostin in allergic inflammation.

CHARACTERISTICS OF PERIOSTIN

Periostin, originally termed osteoblast-specific factor 2, is an ECM protein of 93.3 kDa in size.[6] It belongs to the fasciclin family on its homology to fasciclin 1 (FAS1). Periostin is composed of an EMI domain at the N terminus, four tandemly aligned FAS1 domains in the middle, and splicing domains at the C terminus (Fig. 1). The EMI domain is able to bind to collagen I and fibronectin,[7-9] whereas the FAS1 domains can bind to tenascin-C and bone morphogenetic protein (BMP)-1.[7,8,10] These abilities of periostin as an ECM protein to interact extracellularly with other ECM proteins or proteinase (BMP-1) are assumed to be important in maintaining tissue structure or generating fibrosis.

Since periostin was first isolated from a mouse osteoblast cell line in 1993,[11] our understanding of periostin biology began in osteology.[6,12] It has turned out that periostin contributes critically to bone development/remodeling and bone strength. Expression of periostin is up-regulated during fracture repair or in response to mechanical stress when bone development or remodeling is required. Periostin plays its part by regulating collagen crosslinking and fibrillogenesis by binding to BMP-1 or by binding to Notch 1. Periostin biology has then been extended to the field of cardiology.[6,13] It has been shown that periostin plays a central role in cardiovascular differentiation during *in utero* development of the cardiac valves and fibrous heart skeleton. Even in the postnatal stage, when expression of periostin is low compared to the embryonic stage, periostin expression is rapidly up-regulated in response to insult/injury and is involved in cardiac remodeling. Furthermore, we and others recently showed that upon skin injury, periostin is transiently expressed in granulation tissues and accelerates cutaneous wound repair.[14-16] All of these findings suggest that periostin is a "remodeling" molecule. Thus the significance of periostin in mesenchymal remodeling in various healthy and pathological states has been established.

As periostin biology was becoming better understood, it was revealed that periostin has another face,