Matrix Biology 37 (2014) 150–156

Contents lists available at ScienceDirect

Matrix Biology

journal homepage: www.elsevier.com/locate/matbio

Mini review

# Periostin, a multifunctional matricellular protein in inflammatory and tumor microenvironments

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ARTICLE INFO

Available online 9 May 2014

*Keywords:*
periostin
microenvironment
extracellular matrix
matricellular protein
inflammation
metastasis

ABSTRACT

The behavior and fate of cells in tissues largely rely upon their cross-talk with the tissue microenvironment including neighboring cells, the extracellular matrix (ECM), and soluble cues from the local and systemic environments. Dysregulation of tissue microenvironment can drive various inflammatory diseases and tumors. The ECM is a crucial component of tissue microenvironment. ECM proteins can not only modulate tissue microenvironment but also regulate the behavior of surrounding cells and the homeostasis of tissues. As a nonstructural ECM protein, periostin is generally present at low levels in most adult tissues; however, periostin is often highly expressed at sites of injury or inflammation and in tumors within adult organisms. Current evidence demonstrates that periostin actively contributes to tissue injury, inflammation, fibrosis and tumor progression. Here, we summarize the roles of periostin in inflammatory and tumor microenvironments.



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## 1. Introduction

The extracellular matrix (ECM) is a dynamic structural network and a crucial component of tissue microenvironment. ECM proteins can modulate the microenvironment and regulate the behavior of surrounding cells and the homeostasis of tissues. Tightly controlled ECM homeostasis and remodeling is critical for normal organ homeostasis, wound healing and tissue repair. Matricellular proteins are a group of nonstructural ECM proteins, including thrombospondins, osteonectin, CCNs, tenascins, osteopontin, periostin, TGFBI and others (Bornstein, 1995; Bornstein and Sage, 2002; Wu and Ouyang, 2014). These proteins

*Abbreviations:* AAA, abdominal aortic aneurysm; AD, atopic dermatitis; AHR, airway hyperresponsiveness; BMDC, bone marrow-derived cell; CSC, cancer stem cell; ECM, extracellular matrix; FAK, focal adhesion kinase; IPF, idiopathic pulmonary fibrosis; LOX, lysyl oxidase; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; OSF-2, osteoblast-specific factor 2; TSLP, thymic stromal lymphopoietin; VSMC, vascular smooth muscle cell.

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http://dx.doi.org/10.1016/j.matbio.2014.04.007

are generally present at low levels in most adult tissues, but are highly expressed at sites of injury or inflammation within adult organisms. Matricellular proteins exert several functions by binding to other ECM proteins to remodel the tissue microenvironment, by binding to growth factors and cytokines to modulate their activities, and by interacting with their specific receptors in the cell membrane to regulate signaling inside cells. Accumulating evidence indicates that matricellular proteins play an important role in the inflammatory responses and tumor development (Bornstein and Sage, 2002; Chiodoni et al., 2010; Sorokin, 2010; Wu and Ouyang, 2014).

Periostin, originally named osteoblast-specific factor 2 (OSF-2), was first identified in a mouse osteoblastic cell line as a cell adhesion protein (Takeshita et al., 1993; Horiuchi et al., 1999) and was recently classified as a novel matricellular protein (Norris et al., 2007; Hamilton, 2008; Ruan et al., 2009). The generation of *periostin*-knockout mice provided further insight into its functions in embryonic development (Rios et al., 2005; Kii et al., 2006; Norris et al., 2008). Current studies in animal models and patients demonstrate that periostin is involved in the pathobiology of various diseases, including fibrosis, arthritis, atherosclerosis and other inflammatory diseases, as well as tumorigenesis and metastasis (Ruan et al., 2009; Kudo, 2011; Conway et al., 2014). Emerging data indicate that targeting periostin expression or its related signaling pathways may help us to develop new diagnostic and therapeutic strategies for such diseases. Here, we summarize the roles of periostin in inflammatory responses and tumorigenesis and metastasis and discuss recent insight into the functions of periostin in inflammatory and tumor microenvironments.

## 2. Functions of periostin in inflammation

Inflammation is an immunological response to tissue damage and infection. The immune system senses tissue damage- or pathogen-associated molecular patterns and initiates acute or chronic inflammatory responses. Acute inflammation can be normally terminated and restore the tissue to its homeostatic state when the inducer is cleared, whereas chronic inflammation is prolonged inflammation induced by chronic infection, unhealed tissue damage or persistent allergen (Medzhitov, 2010). Periostin has been reported to be a critical player in the inflammatory microenvironment in various disorders such as airway inflammation, skin inflammation, atherosclerosis and fibrosis (Conway et al., 2014).

### 2.1. Airway inflammation

Asthma is a chronic inflammatory disease of the airways and is characterized by various patterns of cytokine-based airway inflammation. Periostin was identified as an inflammatory effector in bronchial asthma by microarray analysis and can be highly induced upon exposure of human primary bronchial epithelial cells to IL-4 or IL-13 (Yuyama et al., 2002). Further study using bronchial samples and a mouse model of chronic asthma revealed that in asthma, periostin secreted by lung fibroblasts is deposited in the subepithelial fibrosis in the bronchi (Takayama et al., 2006). Epithelial cell-derived periostin in asthma alters collagen fibrillogenesis or cross-linking and results in stiffening of the matrix and alteration of the biomechanical properties of the airway. IL-13-induced periostin in bronchial epithelial cells in asthma has autocrine effects to up-regulate the expression of TGF-β and type 1 collagen through integrins and matrix metalloproteinase (MMP) 2/9 production. Meanwhile, the epithelial cell-derived periostin exerts paracrine effects to induce secretion of type 1 collagen by airway fibroblasts in a TGF-β-dependent manner (Sidhu et al., 2010). Periostin is also involved in a specific type of asthma: eosinophilic airway inflammation. Using an asthma model in which mice are exposed to *Aspergillus fumigatus*, Blanchard et al. (2008) discovered that periostin promotes allergy-induced tissue eosinophilia by increasing eosinophil migration, chemotaxis and adhesion to the ECM components, such as fibronectin. A further clinical study confirmed this observation and suggested that the level of periostin in the peripheral blood of asthma patients can serve as a novel biomarker to select patients for Th2-targeted asthma therapies (Jia et al., 2012). In addition to its role in asthma, periostin is also involved in allergic rhinitis, in which it plays a similar role (Hur et al., 2012). Periostin can be used as a biomarker in idiopathic interstitial pneumonias (Okamoto et al., 2011).

In contrast, two recent papers reported that periostin has a protective role in allergic airway inflammation. *Periostin*-deficient mice exhibit increased airway hyperresponsiveness and high systemic IgE responses. Absence of periostin decreases TGF-β1 and FoxP3 expression in the lung and the epithelial-derived periostin can induce the $FoxP3^+$ regulatory T cell differentiation in vitro in a TGF-β-dependent manner (Gordon et al., 2012). Periostin can also inhibit goblet cell metaplasia and mucus overproduction in asthma (Sehra et al., 2011). Therefore, periostin promotes eosinophilic airway inflammatory responses upon Th2 cytokine stimulation, but it also has a protective role against airway hyperresponsiveness. Further work needs to be conducted to identify the precise mechanism of periostin in airway inflammatory responses.

### 2.2. Skin inflammation

Periostin also has a regulatory role in skin inflammation and fibrosis. Periostin is dynamically and temporally produced during skin development and is strongly related with pathological skin remodeling (Zhou et al., 2010). By using the bleomycin-induced scleroderma mouse model, Yang et al. (2012) discovered that periostin expression is elevated in the skin lesions of scleroderma patients and that periostin can induce procollagen type 1 α1 expression facilitating skin sclerosis by regulating the $\alpha_v$ integrin-mediated PI3K/Akt signaling pathway. Another study revealed that serum periostin level is correlated with severity of skin fibrosis of patients with systemic sclerosis (Yamaguchi et al., 2013). Periostin is highly expressed in the dermis of patients with systemic sclerosis and colocalized with $\alpha$-$SMA^+$ myofibroblasts and $CD31^+$ endothelial cells, indicating that periostin can serve as a biomarker in systemic sclerosis. Periostin is involved in atopic dermatitis (AD), which is a type of allergic skin inflammation. High levels of periostin were detected in the skin tissues of AD patients, and periostin can activate keratinocytes, especially regulating their differentiation and proliferation, through interactions with $\alpha_v$ integrin enhancing Th2 inflammation. Activated keratinocytes in AD produce various proinflammatory cytokines including thymic stromal lymphopoietin (TSLP) acting on immune cells to secret Th2 cytokines, which in turn stimulate periostin production by fibroblasts (Masuoka et al., 2012). Further clinical research reinforces this observation. Serum periostin level is positively correlated with thymus and activation-regulated chemokine, actate dehydrogenase and blood eosinophil count in AD patients (Kou et al., 2014). Therefore, periostin may remodel the ECM and mediate the intracellular $\alpha_v$ integrin pathway and thereby advance skin inflammation, indicating that periostin is a biomarker in AD pathogenesis and is critical for the maintenance and progression of AD.

### 2.3. Atherosclerosis

Atherosclerosis is an inflammatory disease because atherosclerotic lesions are a combination of inflammatory responses (Ross, 1999). Periostin has been identified as an epithelium-derived factor in approximately 90% of advanced atherosclerosis lesions by proteomics and immunohistochemical analyses (Bagnato et al., 2007). Periostin is mainly expressed in the intima, preatheroma regions and ECM of more advanced lesions in human atherosclerotic plaques. Periostin variation is associated with the development of atherosclerosis in young patients through the pathobiological determinants of atherosclerosis study. Multiple variants function together to regulate lesion development (Hixson et al., 2011). Periostin also contributes to atherosclerotic valve degeneration in human and rodents. Periostin, which is mainly secreted