

# Periostin as a biomarker of airway inflammation

Charles McSharry, Steven Johnstone

Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom

The recognition of different asthma phenotypes has helped identify distinct mechanisms of pathogenesis and thereby direct a personalized approach to therapy.<sup>1</sup> Detailed laboratory investigation of these mechanisms has in turn identified distinct inflammatory pathways, or endotypes, which together with phenotype will highlight further molecular targets for therapy and improve patient stratification. Central to this process is biomarker discovery. Periostin is a recognized biomarker in asthma,<sup>3</sup> and is useful for identification of patients with increased clinical benefit from treatment with anti-interleukin (IL)-13 and anti-immunoglobulin-E (IgE) therapy,<sup>3</sup> and may be prognostic for increased risk of asthma exacerbations and progressive lung function decline.<sup>4</sup> It is also a nascent biomarker in chronic obstructive pulmonary disease (COPD).<sup>5</sup> There is a need for further studies in asthma phenotypes and COPD, and in this issue of *Polish Archives of Internal Medicine* (Pol Arch Med Wewn), Katarzyna Górská et al<sup>6</sup> have extended the evaluation of periostin to include steroid-naïve, mild-to-moderate asthma as well as COPD. In a prospective study, they demonstrated that bronchial periostin deposition could be identified by immunohistochemistry in healthy biopsy tissue, that this was progressively greater in COPD and asthma patients, and that the amount of bronchial expression correlated with the periostin concentration in exhaled breath condensate (EBC). Although patient numbers were small, the study was comprehensive and also included periostin concentrations quantified in serum and in airway fluids derived from sputum and lung lavage, although these latter measurements seemed to be of limited clinical value.

Periostin is a vitamin K-dependent,  $\gamma$ -carboxylated protein and a member of the CCN family of matricellular proteins. It was first cloned from a mouse calvarial cell line, hence its original designation as osteoblast-specific factor 2. The human periostin gene (*POSTN*; GenBank accession

number D13664) maps to chromosome 13q13.3 and encodes a secreted 90-kDa protein with an amino-terminal cysteine-rich EMI domain (that binds type I collagen, fibronectin, and Notch1), a tandem repeat of 4 fas1 domains (that bind tenascin C and bone morphogenetic protein 1), and a carboxyl-terminal domain giving rise to multiple alternative splice variants.<sup>7</sup> Together this suggests an extracellular function in cell adhesion and migration, for example, as ligands for  $\alpha V\beta 3$  and  $\alpha V\beta 5$  integrins, binding to the extracellular matrix (ECM) proteins and cell surfaces and enabling attachment and movement.

The periostin literature suggests a common pattern of function based on its localization during tissue development and oncology, response to injury, epithelial-mesenchymal transition, ECM restructuring and remodeling. Normal lung development involves coordinated periostin expression,<sup>8</sup> and experimental models using periostin gene-deleted mice show that periostin is required for normal wound repair<sup>9</sup> and contributes to the pathogenic remodeling in a variety of chronic diseases including broncho-pulmonary dysplasia, bleomycin-induced fibrosis, atherosclerosis, inflammatory bowel disease, and asthma.<sup>10</sup> The serum periostin concentration as a systemic biomarker of local remodeling is increased in idiopathic pulmonary fibrosis<sup>7</sup> and predicts disease progression.<sup>11</sup> Similarly, in severe uncontrolled asthma, the serum periostin concentration is higher in patients with persistent airflow limitation and has an inverse correlation with postbronchodilator forced expiratory volume in 1 second to forced vital capacity ratio despite treatment with high-dose inhaled corticosteroids,<sup>2</sup> and could be a diagnostic tool for targeted therapy against the remodeling component of refractory Th2/eosinophilic asthma inflammation.<sup>4</sup>

Periostin gene expression and protein synthesis is dynamic and rapidly turned over. It is induced by IL-4, IL-13, tumor growth factor (TGF)- $\beta 1$ ,<sup>12</sup> TGF- $\beta 3$ , and by the hypoxia-responsive growth

#### Correspondence to:

Charles McSharry, PhD, FRCPath,  
Institute of Infection, Immunity and  
Inflammation, Room B4/30  
Sir Graeme Davies Building,  
University of Glasgow, 120 University  
Place, Glasgow G12 8TA,  
United Kingdom,  
phone: +44 141 330 2282, e-mail:  
charles.mcsharry@glasgow.ac.uk

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factors angiotensin 11 and fibroblast growth factor 1. In the lungs, periostin expression colocalizes with  $\alpha$ -smooth muscle actin suggesting synthesis by myofibroblasts<sup>8</sup> and periostin expression in airway epithelial cells in asthmatic subjects correlated with the extent of subepithelial fibrosis.<sup>13</sup> Periostin can in turn modulate TGF- $\beta$  function by enhancing airway fibroblast type-1 collagen production and cross-linking and stiffening of the ECM.<sup>13</sup> In addition to this matricellular role, periostin has broader functions relevant to asthma and airway disease. It is a chemotactic factor and provides the appropriate matrix substrate for recruitment of blood eosinophils into the airways.<sup>12</sup> Similarly, periostin is a chemotactic factor for monocyte recruitment from peripheral blood into the tissue environment of tumors via  $\alpha$ V $\beta$ 3 integrin signaling, where they differentiate into M2-type immunosuppressive macrophages.<sup>14</sup> The significance of these macrophages is that they are proremodeling by providing TGF- $\beta$ , which is a chemotactic and activating factor for fibroblasts, and divert arginine metabolism to hydroxyproline production, which supports collagen synthesis. Periostin binding to  $\alpha$ V $\beta$ 3 integrins can activate Akt/PKB signaling to increase cell survival and can activate nuclear factor  $\kappa$ B signaling, which is essential for many immune cell functions, particularly dendritic cells (DCs). Experimental allergic airway inflammation using house dust mite allergen was reduced in a *postn*<sup>-/-</sup> mouse model and this was partly rescued by passive transfer of wild-type *postn*-sufficient DCs,<sup>10</sup> suggesting that periostin may have an immunoregulatory function by providing a matricellular platform for lymphocyte interactions.

The literature above typically supports a strong association between periostin and airway disease; yet there is an emerging literature that periostin might have a protective role in asthma. *Postn*<sup>-/-</sup> mice sensitized with *Aspergillus fumigatus* antigen had increased serum IgE, airway responsiveness, inflammation, and remodeling compared with wild-type mice.<sup>15</sup> The authors suggest that periostin may form a negative-feedback loop regulating allergen-induced responses by augmenting TGF- $\beta$ -induced T-regulatory cell differentiation. Thus the suggestion that periostin itself could be a potential therapeutic in the treatment of atopic disease should be a caution to its use as a therapeutic target as discussed in the final paragraph. In this context of the uncertainty of the role of periostin in airway disease, there is added value in the depth of the study of Górska et al.<sup>6</sup> They unexpectedly found that there was no correlation between airway tissue periostin expression levels and protein concentrations, and this potentially anomalous observation might be informative of a more dynamic role for periostin that has hitherto been unrecognized. It is possible that periostin has a variety of roles operating during different phases of disease, for example, tethering DCs for initial allergen sensitization, then recruiting eosinophils as disease

develops, and finally providing the framework for aberrant remodeling and chronicity. These functions might not be easily demonstrated in cross-sectional studies in patients or in a gene-deleted mouse model, and might explain conflicting findings. It is possible that these different functions are associated with different periostin splice variant isoforms. *POSTN* can undergo alternative splicing in its C-terminal region, generating isoforms that mediate extended  $\beta$ -zipper binding interactions with other proteins during remodeling.<sup>7,16</sup> The function of these unique variants has only begun to be examined and isoform-specific expression has been found in a variety of cell and tissue types, such as in psoriatic arthritis where periostin isoforms are putative biomarkers. Also in idiopathic pulmonary fibrosis (IPF), there is increased gene-level expression differential splicing of periostin that has been associated with clinical progression.<sup>7</sup> A more comprehensive understanding of periostin variant function in asthma and COPD will undoubtedly yield new insight into their pathological processes and reveal potential therapeutic strategies.

One practical point with the study of periostin is that different isoforms may be produced by cells in different tissues and that some anti-periostin antibodies may not necessarily detect all the isoforms. These reasons may help explain the lack of correlation between periostin concentrations found in the different airway samples in the study of Górska et al.<sup>6</sup> There is clearly more work to be done to develop isoform-specific assays, for example, by using liquid chromatography–tandem mass spectrometry, which has shown 3 phosphorylation modification sites of periostin that might further contribute to subtle functional differences.<sup>17</sup> Furthermore, periostin is a  $\gamma$ -carboxylated protein and this has profound effects on protein structure and function, which is still to be explored in periostin. Periostin measurement for evaluating airway disease is more conveniently done using serum<sup>3</sup> rather than using sputum or bronchoalveolar lavage. For example, periostin is a disulphide-linked protein and its immunoreactive detection may<sup>6</sup> or may not<sup>2</sup> be compromised by the use of the reducing agent 0.1% dithiothreitol (DTT) to liquefy sputum plugs. This effect may be mitigated by using a lower DTT concentration or by using less toxic dithioerythritol. The measurement of serum periostin levels in asthma may be compromised by additional periostin synthesis contributed by comorbidities, such as atopic dermatitis. Therefore, the observation of Górska et al.<sup>6</sup> that periostin can be quantified in EBC and that its concentration correlated with airway expression levels suggests that this may become the preferred noninvasive technique.

What are the therapeutic options for targeting periostin? The *in vitro* decellularized aberrant ECM derived from cultured lung fibroblasts from IPF patients, compared with that from non-fibrotic lung tissue, had a greater impact on gene

expression than did cell origin<sup>18</sup>; therefore, targeting matricellular proteins may hold promise for treating the pathogenic remodeling in asthma and COPD. The excess extracellular activity of periostin in the lung may be mitigated by an intervention administered during the remodeling phase of disease. This could be administered by inhalation to avoid affecting its normal function in other tissues. Possible interventions could include humanized periostin-neutralizing antibody, equivalent to OC-20 monoclonal antibodies, replicating *postn*<sup>-/-</sup> mice that have reduced pathogenic remodeling in experimental asthma.<sup>10</sup> Other therapeutics could include the vitamin D analog 22-oxacalcitriol, which might be effective by inhibition of Th2 cytokine- and TGF $\beta$ -induced *POSTN* expression or aptamers that bind to periostin and antagonize its interaction with integrins and inhibit adhesion and migration.<sup>19</sup>

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