Periostin as a marker of mucosal remodelling in chronic rhinosinusitis*

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Abstract

Background: Although extracellular matrix (ECM) proteins are associated with irreversible lower airway changes, the relationship with upper airway remodelling which occurs during chronic rhinosinusitis (CRS) is poorly understood. This study assessed the expression of ECM proteins periostin, fibulin-1, fibronectin and collagenIV in nasal mucosa of patients with and without histologic features of remodelling.

Methods: A cross-sectional study of sinonasal mucosal biopsies taken from patients, undergoing surgery for CRS was performed, where patients were grouped according to remodelling, defined by basement membrane thickening (BMT>7.5µm) and subepithelial fibrosis. An overall view and three random fields of immunostained tissue sections that included epithelium, basement membrane and submucosa, were imaged using Zeiss Zen software. The area and intensity of positive staining were scored by two blinded observers, using a 12-point ordinal scale of weak to strong.

Results: 65 patients (47.6 ± 13.4years, 44.6% female) were assessed. Patients were grouped as controls 26.2%, BMT/no fibrosis 38.5% or BMT and fibrosis 33.8% . Stronger grade of periostin expression was associated with remodelling changes and tissue eosinophilia>10/HPF. Fibulin-1, fibronectin and collagenIV did not differ.

Conclusion: Periostin expression was associated with the presence of BMT, fibrosis and tissue eosinophilia; and may identify patients undergoing remodelling changes.

Key words: extracellular matrix proteins, remodelling, chronic rhinosinusitis, periostin, eosinophils

Introduction

Chronic rhinosinusitis(CRS) encompasses a spectrum of disease with multiple pathogenic factors and inflammatory mechanisms [(1)], some of which are still not fully understood. CRS, especially with nasal polyps or eosinophilia, is particularly difficult to treat, as current successful therapy regimes are designed to gain control, suppress inflammation but not cure [(2-5)].

Chronic lower airway disease is characterized by chronic inflammation which may accompany remodelling events leading to impaired mucosal function. Such changes have been well characterized in the lower airway during progression of chronic diseases such as asthma, which is associated with the release of inflammatory mediators and growth factors and irreversible airway wall thickening [(6)]. However, the remodelling changes which occur during CRS are less well defined.

Inflammation, epithelial fibrosis and basement membrane thickening (BMT) have been shown to be associated with CRS and may be detected using histopathology [(4,7)]. Upper airway remodelling changes have also been shown to be associated with higher prevalence of co-morbid asthma and aspirin sensitivity

in CRS patients. These changes are usually indicative of advanced disease [8-11] and greater treatment requirements [12]. The identification of early mediators of remodelling may aid in the prognosis and appropriate treatment regimes in CRS.
Extracellular matrix proteins (ECM) are involved in physical scaffolding, homeostasis and regulation of inflammation of the airway mucosa [13]. Periostin is induced by IL-4 and IL-13 secreted from airway epithelial cells, resulting in the infiltration of eosinophils and mediating fibrosis [14]. Greater periostin production has been observed in the basement membranes, nasal polyps and infiltrating cells of patients with CRSwNP and aspirin induced asthma [15]. Expression of fibulin-1, fibronectin and collagen in the lower airway has been shown to be associated with asthma [13,16-22]. This study aimed to describe the expression of four ECM proteins, periostin, fibulin-1, fibronectin and collagenIV in CRS; these proteins have previously been implicated in remodelling changes in the lower airway [14,15,18,20,23].

Materials and methods

Study design

A cross-sectional study of patients undergoing endoscopic sinus surgery(ESS) at a tertiary Rhinology practice was performed. Demographic data, smoking status, asthma and structured histopathology [4] were recorded prior to data collection. The study had ethics approval from the local institutional ethics review board (LNR/13/SVH/353).

Patient population

Consecutive consenting patients who underwent endoscopic sinus surgery through a tertiary referral clinic were reviewed. All patients had inflammation identified by histopathology and were grouped according to the presence of remodelling changes as defined by basement membrane thickening (BMT) and subepithelial fibrosis. Patients were divided into three groups, those with only inflammation (controls), those with inflammation and BMT, but no fibrosis, and those who had inflammation, BMT and subepithelial fibrosis. We do not have biopsies from patients with normal mucosa as a separate control group, as our study aims to look at the expression of ECM proteins and their relationship to remodelling of mucosa within CRS patients.No patient used intranasal spray or oral corticosteroids for 4 weeks prior to surgery. Prior cumulative oral corticosteroid use was not accounted for. No patients were taking other immunosuppressive medication. Other medication use was not recorded. Demographic data including age, gender, smoking status, asthma and prior nasal surgeries was recorded. A smoker was defined as a regular current user, or having smoked within the past 12 months. An asthmatic was a person having clinical symptoms of a chronic inflammatory airway disorder needing an inhaled beta-agonist or inhaled prophylactic corticosteroid. Information regarding any previous nasal surgeries was recorded. The pres-

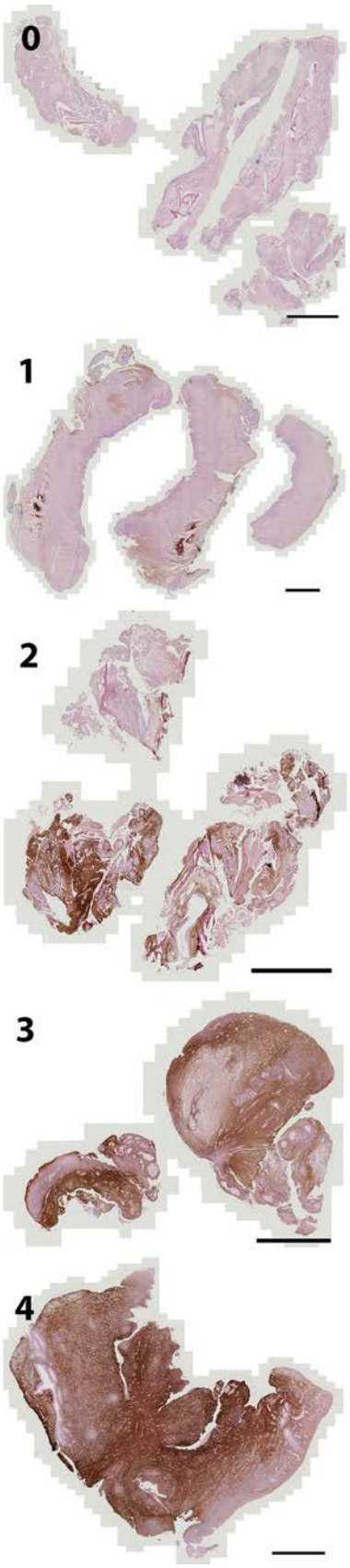

Figure 1. Grading of area of tissue stained positive for periostin by immunohistochemistry (0- No staining, 1- <25% area stained, 2- 25-50%, 3- 50-75%, 4- 75-100%), using an overall view of each slide (the line represents a scale of 2mm).

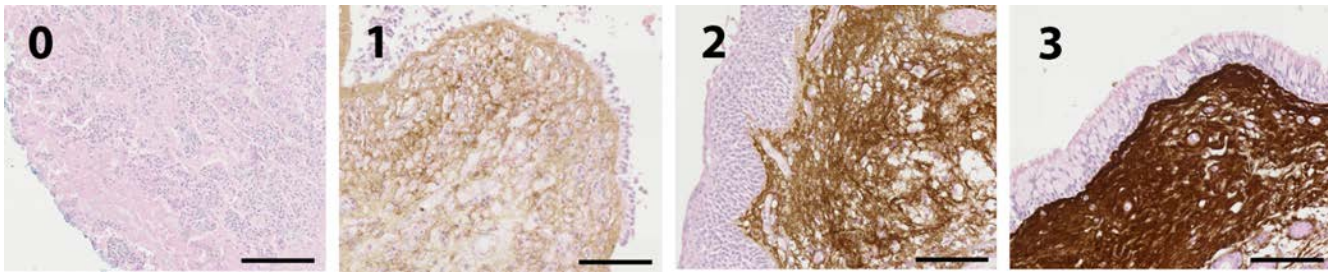

Figure 2. Grading of intensity of staining of periostin by immunohistochemistry (0- No staining, 1- light brown, 2- medium brown, 3- dark brown), using selected fields of view (the line represents a scale of 100μm).

ence of polyps was noted by endoscopic examination.

Remodelling and tissue characterisation

Intraoperative mucosal specimens were taken from the ethmoid sinus and underwent standard haematoxylin and eosin (H&E) staining. Ethmoid mucosa was chosen to best represent the disease process and was selected regardless if simply oedematous or polypoid [24]. Structured histopathology reporting was performed for all patients, based on a previously reported format [4]. Tissue eosinophilia was defined by tissue eosinophil count (>10 per HPF (HPF, 400x), in 2 or more fields) [25]. Remodelling was defined by significant basement membrane thickening (>7.5μm) measured at the site of greatest thickening, and the presence of subepithelial fibrosis, using polarized light to identify areas of excess collagen deposition [4]. These changes have been demonstrated in CRS with greater treatment implications [7,12].

Immunohistochemical staining for periostin, fibulin-1, fibronectin, collagenIV was performed on serial 5μm thick paraffin embedded formalin fixed sinus mucosa. Fibulin-1 and periostin staining was performed following the protocol described previously by Jaffar et al. [26] while fibronectin and collagen IV staining was performed using a protocol adapted from Faiz et al. [27] with slight modifications. In summary, the sections were deparaffinized and rehydrated through xylene and decreasing concentrations of ethanol (2 x 100%, 95%, 70%, 50% ethanol) into deionized water prior to antigen retrieval. No antigen retrieval was required for fibronectin, periostin and fibulin-1 while collagenIV required treatment for 30 mins in 0.5% Trypsin in PBS solution at 37°C followed by 3x5 minute washes in deionised water. The sections were incubated with peroxidase blocking solution (Dako, Glostrup, Denmark) followed by non-immune protein block (Dako). Primary antibody (periostin: 0.5 μg/mL, fibulin-1: 0.05 μg/mL, fibronectin: 0.2 μg/mL and collagenIV: 1.0 μg/mL) and isotype control antibody (same concentration as the respective primary antibodies) diluted in Antibody Diluent (Dako) on serial sections were then incubated for 2 hours at 37°C (fibulin-1 and periostin) or overnight at 4°C (Fibronectin and CollagenIV) before being washed 5 times in TBS-T for 3 minutes each, followed by incubation in horseradish peroxidase (HRP)-conjugated secondary antibody (Dako) for 45 minutes in an incubator at 37°C. The sections were then washed 5 times in TBS-T for 3 minutes each and the 3, 3'- Diaminobenzidine (DAB) chromogen was applied for 10 minutes. Following DAB incubation the sections were washed 5 times in deionized water and then counterstained by immersion in Mayer's haematoxylin (Sigma Aldrich, St Louis, MI, USA) for 5 minutes. After washing in tap water for 2 minutes the sections were then dehydrated through 70% ethanol for 30 secs, counterstained with eosin Y for 1 minute, quick dips in 95%, 100% and 100% ethanol and 2 changes of xylene prior to coverslipping with dibutyl phthalate in xylene (DPX) organic mounting media (Asia Pacific Specialty Chemicals, Seven Hills, NSW, Australia).

Images were captured using a Wide-field FL and TL microscope ZEISS Axio Scan.Z1 Slide Scanner (Zeiss, Oberkochen, Germany). The immunostained tissue was scanned at 20x magnification and a whole brightfield tissue image was stitched together from the individual serial images using ZEN software (Zen 2012, Carl Zeiss Microscopy GmbH).

Scoring system

The slides for each stain were viewed and scored independently by two blinded observers. A single view of the entire tissue section was used to assess the Area (A) of the tissue stained positive for each ECM protein, and scored on a 5 point ordinal scale(0- No staining, 1- <25% area stained, 2- 25-50%, 3- 50-75%, 4- 75-100%) (Figure1).

The intensity (I) of staining of each ECM protein was scored using a 4 point ordinal reference scale (0- No staining, 1- light brown, 2- medium brown, 3- dark brown) (Figure2). The intensity score focused on the intensity of stain at the level of the basement membrane and in the submucosal region, as these were our areas of interest. All slides were first randomly viewed before areas representative of each level of intensity were chosen for the scale. Three random fields (at 35% zoom on a 20x magnified image) in which there was a good view of the epithelium, the basement membrane and the submucosa were chosen for each

slide and scored independently by the two blinded observers. Fields of view covering the same three areas of each patient's tissue sections were scored for all the four stains.
An overall 'Grade of staining'(G) was assigned to each slide by multiplying Area x Intensity (G = A x I)(Grade: 0-12, 0 being no staining and 12 being the strongest staining). These grades were predetermined prior to assessment.

Statistical analysis

Statistical analysis was performed using IBM® SPSS Statistics version 20.0. Age was parametric and presented as mean (± standard deviation [SD]) and analysis was an ANOVA between groups. Descriptive data are reported as percentages, Kendall's tau-B was used for relationships between ordinal values and the Chi-square test was used for nominal variables. The grade of staining was ordinal and assessed with Kendall's tau-B. The intra-class correlation coefficient (two-way mixed effect model) was used to assess reliability of scoring between the two independent reviewers. Probability values (p-value) ≤0.05 were considered statistically significant.

Results

Demographics

Sixty-five patients, 47.67 ± 13.4 years, 44.6% female, were assessed. Half (50.8%) were asthmatic, 6.2% were smokers, 60% had prior sinonasal surgery, 46.2% had nasal polyps and tissue eosinophilia was present in 56.9% of patients. The baseline differences between the three groups are described in Table1. Asthma status was similar across the groups (47.1% v 60% v 45.5%, p=0.56), as was smoking status (0% v 12% v 4.5%, p=0.27). A number of patients had prior surgery (82.0% v 52.0% v 54.5%, p=0.11), and tissue eosinophilia >10/HPF (47.1% v 60.0% v 63.6%, p=0.56), although the distribution across groups was not significant.
Tissue eosinophilia >10/HPF was significantly associated with the presence of polyps (83.3% of polyps having eosinophilia v 34.3% of non-polyps with eosinophilia, p<0.01) and asthma(62.2% of asthmatics having eosinophilia v 35.7% of non-asthmatics with eosinophilia, p=0.04). The frequency of prior surgery was higher in patients with polyps (73.3%of revision patients had polyps v 48.6% of primary surgical cases, p=0.05) but not significantly associated with tissue eosinophilia (67.6% of revision patients had tissue eosinophilia vs 50.0% without, p=0.15)(Table3).

Association between grade of staining and remodelling changes

Grade of expression of periostin (Strong: 47.1% v 48.0% v 68.2%, p=0.05) was significantly associated with remodelling changes, however, it was similar between the groups for fibulin-1 (Strong: 47.1% v 36.0% v 36.4%, p=0.80), fibronectin(Strong: 52.9% v 56.0% v 50.0%, p=0.74) and collagenIV (Strong: 17.6% v 20.0% v 28.6%, p=0.87)(Table2).

Table 1. Allocation of baseline demographics between groups based on remodelling.

	Remodelling changes % (n)			p value
	Only inflammation (controls)	Inflammation+ BMT+ No fibrosis	Inflammation+ BMT+ Fibrosis+	
n	17	25	22	
Age	48.72 (±14.21)	48.45 (± 12.32)	47.13 (± 13.76)	0.91
Gender (%F)	52.9% (9)	48.0% (12)	36.4% (8)	0.55
Asthma	47.1% (8)	60.0% (15)	45.5% (10)	0.55
Smokers	0% (0)	12.0% (3)	4.5% (1)	0.27
Polyps present	41.2% (7)	44.0% (11)	54.5% (12)	0.66
Tissue eosinophilia >10/HPF	47.1% (8)	60.0% (15)	63.6% (14)	0.56
Prior Surgery	82.4% (14)	52.0% (13)	54.45% (12)	0.11

Table 2. Association of grade of expression of extracellular matrix proteins with remodelling changes (% displayed is the proportion of patients with a strong staining grade 7-12). Analysis was performed as a Kendall-Tau B with all 0-12 ordinal categories/grades of staining expression. Sub-grouping is for demonstration of summary data only.

ECM protein	Remodelling changes % (n)			p value (Kendall's tau-B)
	Only inflammation (controls)	Inflammation+ BMT+ No fibrosis	Inflammation+ BMT+ Fibrosis+	
Periostin	47.1% (8)	48.0% (12)	68.2% (15)	0.05
Fibulin-1	47.1% (8)	36.0% (9)	36.4% (8)	0.80
Fibronectin	52.9% (9)	56.0% (14)	50.0% (11)	0.74
CollagenIV	17.6% (3)	20.0% (5)	28.6% (6)	0.87

Association of grade of staining with tissue eosinophilia

Both periostin (Strong: 67.6% with tissue eosinophilia v 39.3% without, p=0.01) and fibronectin (Strong: 67.6% v 32.1%, p=0.05) showed significantly increased staining in patients with tissue eosinophilia, although fibulin-1 (Strong: 37.8% v 42.9%, p=0.81) and collagenIV (Strong: 24.3% v 18.5%, p=0.41) were not found to differ (Table3).

Intra-class correlation coefficient (ICC)

There was good agreement between the two independent observers; ICC for periostin (0.90), fibulin-1 (0.77), fibronectin

Table 3. Correlation of Tissue Eosinophilia >10/HPF with baseline demographics and strong grade of expression of extracellular matrix proteins.

	Tissue eosinophilia %(n)		
	<10/HPF	>10/HPF	p-value
n	28	37	
Age	45.37(±13.43)	49.42(±13.32)	0.23
Gender (%female)	46.4%(13)	43.2%(16)	0.80
Asthma	35.7%(10)	62.2%(23)	0.04
Smoking	3.6%(1)	8.1%(3)	0.45
Prior Surgery	50.0%(14)	67.6%(25)	0.15
BM thickening	64.3%(18)	78.4%(29)	0.21
Fibrosis	28.6%(8)	37.8%(14)	0.43
Polyps present	17.9%(5)	67.6%(25)	<0.01
Periostin (≥strong grade)	39.3%(11)	67.6%(25)	0.01
Fibulin-1 (≥strong grade)	42.9%(12)	37.8%(14)	0.80
Fibronectin (≥strong grade)	32.1%(9)	67.6%(25)	0.05
CollagenIV (≥strong grade)	18.5%(5)	24.3%(9)	0.41

Table 4. Association of grade of expression of extracellular matrix proteins with remodelling changes in primary cases (% displayed is the proportion of patients with a strong staining grade 7-12). Analysis was performed as a Kendall-Tau B with all 0-12 ordinal categories/grades of staining expression. Sub-grouping is for demonstration of summary data only.

ECM protein	Remodelling changes in primary cases % (n)			p value (Kendall's tau-B)
	Only inflammation (controls)	Inflammation+ BMT+ No fibrosis	Inflammation+ BMT+ Fibrosis+	
Periostin	33.3%(1)	33.3%(4)	70.0%(7)	0.05
Fibulin-1	66.7%(2)	25.0%(3)	40.0%(4)	0.50
Fibronectin	0%(0)	50.0%(6)	50.0%(5)	0.53
CollagenIV	33.3%(1)	16.7%(2)	33.3%(3)	0.77

(0.91), collagenIV (0.91) with p<0.01.

Analysis on primary (unoperated) surgical cases

A separate sub-analysis was done on only primary surgical cases (n=26), with age 42.52 ± 12.88, 42.3% female. Asthma was present in 42.3%, smoking (11.5%), polyps (30.8%), tissue eosinophilia >10/HPF (46.2%) of primary cases. Tissue eosinophilia >10/HPF was significantly associated with polyps (50.0% with tissue eosinophilia v 14.3% without, p=0.05), basement membrane thickening (100% v 71.4% p=0.04]) and fibrosis (58.3% v 21.4%, p=0.05).

Table 5. Allocation of baseline demographics between groups based on primary cases versus previously operated cases.

	Primary cases %(n)	Previous surgeries %(n)	p-value
N	26	39	
Age	42.52(±12.88)	51.10(±12.80)	0.75
Gender (%f)	42.3%(11)	46.2%(18)	0.09
Asthma	42.3%(11)	56.4%(22)	0.30
Smoking	11.5%(3)	2.6%(1)	0.29*
BM thickening	84.6%(22)	64.1%(25)	0.07
Fibrosis	38.5%(10)	30.8%(12)	0.52
Tissue eosinophilia >10/HPF	46.2%(12)	64.1%(25)	0.15
Presence of polyps	30.8%(8)	56.4%(22)	0.04

*Fisher's Exact Test, given expected cell count less than 5

Table 6. Association of grade of expression of extracellular matrix proteins with primary cases and those who had previous surgery(% displayed is the proportion of patients with strong staining grade 7-12). Analysis was performed as a Kendall-Tau B with all 0 -12 ordinal categories/grades of staining expression. Sub-grouping is for demonstration of summary data only.

ECM protein	Primary cases %(n)	Previous Surgery %(n)	p value Kendall's tau-B
Periostin	50.0%(13)	59.0%(23)	0.98
Fibulin-1	38.5%(10)	41.0%(16)	0.52
Fibronectin	42.3%(11)	59.0%(23)	0.27
CollagenIV	24.0%(6)	20.5%(8)	0.49

The grade of expression of the four ECM proteins, showed similar relationships to the overall analysis, with periostin (Strong: 33.3% v 33.3% v 70.0%, p=0.05), fibulin-1(Strong: 66.7% v 25.0% v 40.0%, p=0.50), fibronectin (0% v 50.0% v 50.0%, p=0.53) and collagenIV (Strong: 33.3% v 16.7% v 33.3%, p=0.77)(Table 4). Also, higher periostin grade was significantly associated with tissue eosinophilia (Strong: 66.7% with tissue eosinophilia v 35.7% without, p<0.01). There were no significant differences in ECM protein expression between primary and previously operated cases (Table 5 and 6).

Discussion

Remodelling of the respiratory mucosa is a feature of patients

with airway disease [2]. Chronic airway remodelling represents an aberrant repair cycle with the interaction between many cell types, including epithelial cells, fibroblasts and smooth muscle cells. The "epithelial-mesenchymal trophic unit" is thought to drive chronic remodelling in asthma. In asthma, the airway wall is thickened with epithelial dysplasia, angiogenesis, increased extracellular matrix (ECM) deposition, and increased airway smooth muscle (ASM) mass. These changes are thought to contribute to increased airflow obstruction that is only partially reversed by therapy and may lead to an element of fixed airflow obstruction. The severity of asthma correlates with the presence of remodelling [28-30].

There are several articles in literature that describe increased inflammatory cell infiltrate and increased thickness of the basement membrane as part of remodelling changes in the asthmatic airway as compared to normals. Ward et al, in 2002, described subepithelial reticular basement membrane thickening and inflammatory cells significantly increased in asthmatics as compared to normals [30]. When compared with healthy volunteers, Chetta et al found that patients with asthma had significantly higher levels of mast cells, activated eosinophils, basement membrane thickening and vascular area [31]. In 2007, Bourdin et al. used two different techniques to measure the reticular basement membrane, and found that there was significant thickening of the basement membrane, not just in severe asthma, but even in mild asthma as compared to normal healthy controls [32]. Increased expression of periostin [14], fibulin-1 [18,23], fibronectin [17,20] and decreased collagenIV [33,34] have also been associated with remodelling changes in the lower airway of asthmatics as compared to normals. As our study aims to look at the expression of ECM proteins and their relationship to remodelling of mucosa in CRS patients, we did not study mucosa from normal patients as a separate control group.

While remodelling exists in CRS [7] its impact on disease outcomes is less clear than in the asthma literature. Prior studies have demonstrated a relationship between BM thickening and duration of symptoms [35], the presence of eCRS [7] and the need for more ongoing therapy [12].

There is prior evidence in literature that periostin plays an important role in inflammation and remodelling of the nasal mucosa in CRS, through the activation and chemotaxis of eosinophils [15,36]. Ishida et al. described periostin positive staining in the basement membrane, ECM, inflammatory cells and tissue from nasal polyps by immunohistochemistry. Their study also found significantly higher levels of periostin in tissue from patients with allergic rhinitis, CRSwNP and aspirin-induced asthma than in controls [15].

The 'grade' of expression used in this study is a reflection both of the area of the tissue stained positive for the protein, as well as the intensity of the stain. A higher grade of periostin expression was found in the group with both BMT and fibrosis. Increased periostin was significantly associated with the presence of remodelling changes, in keeping with known literature.

The evidence that periostin concentration, in tissue, serum or sputum, and the numbers of eosinophils are closely related is supported by the high expression of periostin in patients with tissue eosinophilia [37,38]. The cause-effect relationship of periostin and eosinophilia is something of a causality dilemma. Johansson et al. identified αMβ2, a periostin receptor which is expressed by activated eosinophils [39]. Li et al. have suggested that an autocrine loop involving periostin and eosinophils could lead to a vicious cycle of signalling and its effects [40]. The association of periostin with tissue eosinophilia and remodelling changes may provide an early indication of the severity of the disease [7]. Tissue eosinophil status and remodelling were used to assess groups rather than polyp status. The phenotype of severe oedema, polypoid mucosa and frank polyps is ambiguous and difficult to define, especially in the revision patient and was avoided.

Periostin, originally named osteoblast specific factor, may also have a role in the neo-osteogenesis which occurs in CRS [41]. Tissue eosinophilia has also been shown to be associated with bone remodelling changes [42]. Matsusaka et al. recently reported high concentrations of serum periostin correlated with a specific phenotype of late onset eosinophilic asthma unresponsive to inhaled corticosteroids, and associated with CRSwNP and olfactory dysfunction [43]. Detection of serum or sputum periostin may be an easier way of identifying patients with a more resistant phenotype [37].

The grade of expression was similar between groups for fibulin-1, fibronectin and collagenIV. Lau et al. have reported increased levels of fibulin-1 in asthmatics and shown its potential role in airway remodelling [18]. Increased levels of fibronectin have been reported in the airways of patients with asthma [17]. The role of eosinophil secreted profibrotic cytokines like TGF-β and the deposition of collagen have been reported [16,19-21]. Van Bruaene et al have reported early collagen deposition in sinus disease even before the advent of inflammation [44].

Fibrosis is typically measured by the histological assessment of the overall expression of all collagens. There are at least 29 different types of collagens, each of which has multiple genetically distinct alpha chains. In this study, we looked at one specific type of collagen, collagenIV, found in basement membranes, based on the investigators' previous publications in which collagenIV was found to be significantly decreased in patients with asthma [33,34]. Other collagen subtypes are likely to account for fibrosis where collagenIV was not expressed.

Van Zele et al. describe the different expression of cytokines in recurrent versus non-recurrent CRSwNP [45]. In 2016, Tomassen et al. described a wide variety of endotypes of CRS based on inflammatory profiles [46].

While extracellular matrix proteins are normally present in

tissues, only periostin showed statistically significant association with remodelling and tissue eosinophilia. This finding is consistent with published literature, and supports evidence that increased expression of periostin is likely to be important in the pathophysiology of CRS. However, the other ECM proteins may have some relationship with remodelling changes but a Type 2 error may exist. Zhang et al. demonstrated a decrease in the expression of periostin in sinus tissue three months after successful therapy, suggesting that periostin expression may reflect disease activity [47]. Thus, ECM proteins may have a potential to serve as early biomarkers of remodelling changes in the nasal and sinus mucosa. The ease of detection of ECM proteins, especially periostin, has improved over recent years, with immunohistochemistry, microarray analysis of gene expression, detection of serum and sputum expression all available, making the ECM proteins valuable in their role both as prognostic indicators and future targets for modifying disease.

Although this study demonstrated a relationship with periostin expression and remodelling, changes in expression of the ECM proteins with disease progression or as a response to therapy are areas of interest yet to be addressed. Such mucosal remodelling changes might predict a degree of 'fixed' mucosal change and limited reversibility of the disease process. Early therapy may be warranted in patients at risk of mucosal remodelling, and such an approach might explain the more favourable outcomes in patients who are treated more aggressively in their disease course [48]. Further studies involving a larger number of patients, with follow up, would be required to explore the influence of ECM proteins on disease management and/or early detection.

Conclusion

Extracellular matrix proteins, especially periostin, are increasingly being studied as mediators of inflammation and remodelling, both in the lower and the upper airway. A higher grade of periostin expression was significantly associated with the presence of remodelling changes and tissue eosinophilia. ECM proteins such as periostin may serve as early prognostic indicators of eosinophil activation and remodelling, heralding more aggressive therapy or as targets for disease modifying strategies.

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Authorship contribution

JAE: study design, data collection and analysis, manuscript draft and edits; JMC: data collection and analysis, manuscript draft and edits; BGO: study design, data collection and analysis, manuscript edits, expert opinion; RAO: data collection and analysis; GT: data collection and analysis, manuscript draft and edits; JH: data collection and analysis; ARH: data collection and analysis; JR: study design, data collection and analysis, manuscript edits, expert opinion; RS: manuscript edits, expert opinion; RJH: conceptualization, study design, data collection and analysis, manuscript edits, expert opinion.

Conflict of interest

RJH is consultant with Medtronic, Olympus and NeilMed pharmaceuticals. Research grant funding received from Meda Pharmaceuticals and Stallergenes. Has been on the speakers' bureau for Glaxo-Smith-Kline and Arthrocare. RS is a consultant with Medtronic and Takeda pharmaceuticals.

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