Involvement of the Extracellular Matrix Proteins Periostin and Tenascin C in Nasal Polyp Remodeling by Regulating the Expression of MMPs

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Research

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Abstract

Background: Tissue remodeling caused by increased MMPs is involved in the pathogenesis of chronic rhinosinusitis with nasal polyposis (CRSwNP). We previously found higher levels of periostin and tenascin C in CRSwNPs, but whether they are associated with the dysregulation of MMPs is unknown. Therefore, the present study aimed to investigate the regulatory roles of two ECM proteins in the expression of MMPs in nasal polyps.

Methods: The concentrations of MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13, TIMP-1, TIMP-2, TIMP-3, TIMP-4, periostin, and tenascin C in tissue homogenates of 51 patients with chronic rhinosinusitis with and without nasal polyps and 15 control subjects were measured and their correlations were analyzed. Primary human nasal polyp fibroblasts and epithelial cells were stimulated ex vivo with periostin and tenascin C and the gene expression of MMPs and TIMPs was determined by means of real-time PCR.

Results: The protein levels of MMP-3, MMP-7, MMP-8, MMP-9, TIMP-1, TIMP-2, periostin, and tenascin C were significantly higher in patients with CRSwNPs than in healthy control subjects. Periostin was positively correlated with MMP-3 and TIMP-2, and tenascin C was positively correlated with MMP-3, MMP-7, MMP-8, MMP-9 and TIMP-2. Periostin stimulated the gene expression of MMP-3, MMP-7, and MMP-9 in fibroblasts and MMP-7 in epithelial cells ex vivo. Tenascin C stimulated the expression of MMP-3, MMP-8, and MMP-9 in epithelial cells, but not in fibroblasts. The expression of TIMPs in fibroblasts and epithelial cells was affected by neither periostin nor tenascin C.

Conclusions: Periostin and tenascin C might be involved in the remodeling of nasal polyps by regulating the expression of different MMPs in epithelial cells and fibroblasts. Our findings have the potential to identify key factors of tissue remodeling in CRSwNPs.

Background

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a complex inflammatory disease in the upper airways, characterized by the formation of edematous stroma and pseudocysts.[1] Evidence shows that tissue remodeling is one of the main causes of the formation of nasal polyps.[2] Tissue remodeling within nasal polyps (NPs) involves extracellular matrix (ECM) accumulation and degradation. Matrix metalloproteinases (MMPs)[3] are proteases that can degrade the ECM and modify the tissue structure. Higher levels of MMPs in NPs contribute to expansive histologic changes in nasal polyps,[4, 5] which can be inhibited by the tissue inhibitors of metalloproteinase (TIMPs). The levels of MMPs and its inhibitor TIMPs are involved in the pathogenesis of CRSwNPs.[6]

MMP-induced tissue remodeling is strongly associated with ECM proteins, which play diverse roles and modulate cell-matrix interactions to control cellular metabolism within the ECM.[7] The ECM proteins are readily up-regulated under pathological conditions.[8] We previously found higher levels of the ECM proteins, tenascin C and periostin, in NPs compared with controls.[9] Periostin is a confirmed novel
biomarker for the formation of nasal polyps and tenascin C is an indicator of inflammation.[7, 10] However, whether the two ECM proteins contribute to the formation of CRSwNP via tissue remodeling is unknown. Given that the levels of MMPs in NP tissues are elevated,[5, 11, 12] and there is evidence supporting the association between the two ECM proteins (periostin and tenascin C) and the expression of MMPs beyond nasal mucosa[13–15]. We hypothesized that periostin and tenascin C might have an impact on the expression of MMPs in NPs.

Fibroblasts and nasal epithelial cells are key-effector cells in tissue remodeling, which can stimulate the tissue remodeling process in NPs by the expression of matrix metalloproteinases (MMPs).[16, 17] As ECM proteins are able to control cellular behavior and the two ECM proteins, periostin and tenascin C, are associated with the expression of MMPs, we hypothesized that periostin and tenascin C stimulate the expression of MMPs in fibroblasts and epithelial cells. Thus, we tested the levels of tissue remodeling factors and investigated whether periostin and tenascin C stimulate the expression of MMPs via nasal fibroblasts and epithelial cells in NP.

Methods

Patients

The study enrolled 66 subjects from the Rhinology Department of Beijing Tongren Hospital affiliated with Capital Medical University, including 14 patients with chronic rhinosinusitis without nasal polyposis (CRSsNP), 37 patients with CRSwNP, and 15 control subjects. These subjects were the same as in a previously published study.[9] The diagnosis of chronic rhinosinusitis (CRS) was in accordance with the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012).[18] None of the study subjects had any history of malignancy, cystic fibrosis, ciliary dyskinesia, allergic fungal sinusitis, maxillary antrochoanal polyps, or autoimmune diseases. Tissue samples were obtained from the inferior turbinates of the control subjects, the ethmoid mucosae of patients with CRSsNP, and the NPs of patients with CRSwNP. These samples were frozen and stored at -80 °C until used for immunoassays.

Immunoassay

Tissue homogenates were prepared as previously described.[19] Briefly, frozen nasal tissues were weighed and homogenized with an automated homogenizer (TissueLyser LT; Qiagen, Dublin, Ireland) for 2 minutes. The homogenates were then dissolved in 0.9% NaCl (1 mL of 0.9% NaCl per 0.1 g of tissue) with 1% protease inhibitor cocktail (Sigma-Aldrich, St Louis, Mo) and centrifuged to collect the supernatants.

The prepared tissue homogenates were assayed for tenascin C (US Biological, Salem, MA, USA), periostin, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and TIMP-1, TIMP-2, TIMP-3, and TIMP-4 (R & D Systems, Minneapolis, MN) by commercially available kits.
Primary human nasal polyp fibroblasts cell culture and ex vivo stimulations

Fibroblasts in nasal polyps were isolated based on a previously described method.[20] Briefly, fresh nasal polyp samples were obtained from CRSwNP patients and were washed several times with phosphate-buffered saline (PBS), supplemented with 200 U/mL penicillin and 200 U/mL streptomycin. Samples were diced and plated in 100-mm tissue culture plates containing HyClone RPMI 1640 medium with 10% fetal bovine serum (FBS; Gibco) and 100U/mL of penicillin and streptomycin. When a monolayer of fibroblast-like cells was found to be confluent, the cells were digested and passaged. After three passages, the cells were stimulated with 1ug/mL, 2ug/mL, and 5ug/mL of periostin or tenascin C for 24 h, with the culture medium used as the control. The collected cells were stored at -80 °C for further gene expression detection. The cells were characterized by flow cytometry using anti-human CD90-FITC and anti-human CD45-PerCP antibodies (Miltenyi Biotech) as previously described.[21] The purity was more than 96%.

Primary human nasal polyp epithelial cells culture and ex vivo stimulations

Nasal polyp epithelial cells were established according to a previously described method.[22] Briefly, fresh nasal polyp samples were rinsed with PBS and digested in 1 mg/mL protease (Protease from Streptomyces griseus, Type XIV; Sigma-Aldrich) for 1 hour at 37 °C. Cell suspensions were centrifuged at 800 rpm for 5 min and resuspended in bronchial epithelial growth medium (BEGM, Lonza, Basel, Switzerland). Cells were plated for 1 hour on 100-mm tissue culture plates to remove contaminating fibroblasts. The isolated cells were seeded on rat-tail collagen-coated tissue culture plates at 37 °C with 5% CO₂. The culture medium was changed every other day until the cells reached confluence. The isolated nasal epithelial cells were trypsinised and seeded into 12-well culture plates at a concentration of 5 × 10^5 cells/mL in 1 mL BEGM with 10% FBS and 100U/mL of penicillin and streptomycin. After reaching 80% confluence, the cells were stimulated with 1ug/mL, 2ug/mL, and 5ug/mL of periostin or tenascin C for 24 h, with the culture medium used as the control. The collected cells were stored at -80 °C for further gene expression detection.

Real-Time PCR

Total RNA from unstimulated and stimulated fibroblasts and epithelial cells was extracted using TRIzol reagent (Ambion-Life Technologies, Carlsbad, Calif). The RNA was reverse transcribed into first-strand cDNA with random primer, and real-time polymerase chain reaction (PCR) was subsequently performed using the ABI7500 PCR system (Applied Biosystems, Foster City, Calif). Primer sequences are given in Table 1. The PCR conditions were as follows: a 95 °C denaturation step for 10 minutes followed by 40 cycles of 95 °C denaturation (15 seconds) and 60 °C annealing (1 minute). Gene expression was normalized to the housekeeping gene β-actin. The comparative cycle threshold (Delta Delta Ct) method was used for relative gene expression analysis.
Table 1
Primers used for quantitative RT-PCR analysis.

| Primer | Sequence                      | AT (°C) |
|--------|-------------------------------|---------|
| MMP-3  | (F) 5’-AGGCTGTATGAAGGAGAGGCTGAT-3’ | 60      |
|        | (R) 5’-AGTGTTGGCTGAGTGAAAGAGACC-3’ |         |
| MMP-7  | (F) 5’-TGTATGGGGAACTGCTGACA-3’ | 60      |
|        | (R) 5’-GCGTTCATCCTCATTCAAGT-3’ |         |
| MMP-8  | (F) 5’-CCTTGCTAAGGACTACTGGGC-3’ | 60      |
|        | (R) 5’-CTGGCCCATTTGGGTTTGA - 3’ |         |
| MMP-9  | (F) 5’-GCCGACTTTTTTGTGGTCTTCC-3’ | 60      |
|        | (R) 5’-TACAAGTATGCTCTG GCCAGC-3’ |         |
| TIMP-1 | (F) 5’-CTGTGGTTGCTGTGGCTGAT-3’ | 60      |
|        | (R) 5’-ACTTGGCCCTGTAGCAGGAGC-3’ |         |
| TIMP-2 | (F) 5’-CGTTTTGCAAATGCAGATGTA-3’ | 60      |
|        | (R) 5’-TCCTCTTGATAGGGTTGCCA-3’ |         |
| β-actin| (F) 5’-GATCCACATCTGCTGGAAGG-3’ | 60      |
|        | (R) 5’-AAGTGACGGTCTGACGTTCC-3’ |         |

At, annealing temperature

Statistical Analysis

All statistical data were analyzed using IBM SPSS Statistics, Version 21.0 (IBM Corp, Armonk, NY, USA). A Kolmogorov–Smirnov test was used to analyze the data distribution and the Kruskal-Wallis test was used for multiple comparisons among the different groups. When the results were significantly different, the Mann-Whitney U test was used for inter-group comparison. Relationships between the various parameters were evaluated by Spearman correlation analysis. The Wilcoxon matched pairs test was used to compare the gene expression of patients-matched unstimulated and stimulated nasal polyp-derived fibroblasts and epithelial cells.

Results

Expression of MMPs, TIMPs and ECM proteins in nasal tissue homogenates from patients with CRSsNP and CRSwNP
The protein levels of MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and TIMP-1, TIMP-2, TIMP-3, TIMP-4 were examined in tissue homogenates from patients with CRS. Figure 1 shows the results. In comparison with healthy control subjects, no difference was found in patients with CRSsNP for all these MMPs and TIMPs, while increased levels of MMP-3, MMP-7, MMP-8, MMP-9 and TIMP-1, and TIMP-2 were found in patients with CRSwNP. The levels of MMP-8 and MMP-9 were higher in patients with CRSwNP than in patients with CRSsNP, but the level of TIMP-1 was lower.

Figure 2 shows that in comparison to healthy control subjects, both periostin and tenascin C were up-regulated in patients with CRSwNP, but not in patients with CRSsNP. Additionally, significantly higher levels of tenascin C were found in patients with CRSwNP versus patients with CRSsNP.

Correlations between MMPs and TIMPs and ECM proteins.

Since higher levels of MMP-3, MMP-7, MMP-8, MMP-9, TIMP-1, TIMP-2, periostin and tenascin C were found in patients with CRSwNP, we investigated the correlations between these MMPs and TIMPs and the ECM proteins. As shown in Table 2, periostin was positively correlated with MMP-3 and TIMP-2, and tenascin C was positively correlated with MMP-3, MMP-7, MMP-8, MMP-9 and TIMP-2 in all subjects. Moreover, periostin tended to be positively correlated with MMP-9 with a p value of 0.053.

| Table 2 | Correlations of the protein levels of periostin and tenascin C with MMPs and TIMPs in nasal tissue homogenates from all subjects. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
|         | Periostin | Tenascin C | r value | p value | r value | p value |
| MMP-3   |           |           | 0.334    | 0.006   | 0.502   | <0.001  |
| MMP-7   |           |           | 0.192    | 0.192   | 0.318   | 0.009   |
| MMP-8   |           |           | 0.222    | 0.222   | 0.438   | <0.001  |
| MMP-9   |           |           | 0.239    | 0.053   | 0.425   | <0.001  |
| TIMP-1  |           |           | -0.13    | -0.13   | -0.132  | 0.289   |
| TIMP-2  |           |           | 0.251    | 0.042   | 0.453   | <0.001  |

Effect of periostin and tenascin C treatment on the gene expression of MMPs and TIMPs in nasal polyp-derived primary fibroblasts ex vivo
Regarding the correlations of ECM proteins with the expression of MMPs and TIMPs, and the fact that fibroblasts are the main source of MMPs and TIMPs, we first observed the regulation by ECM proteins of MMP-3, MMP-7, MMP-8, MMP-9 and TIMP-1, and TIMP-2 gene expression in nasal polyp-derived fibroblasts. The results showed that periostin treatment significantly increased the expression of MMP-3, MMP-7 and MMP-9, but had no effect on the expression of MMP-8, TIMP-1 and TIMP-2 (Fig. 3). However, tenascin C treatment did not change the expression of any of these MMPs and TIMPs at the gene level in the fibroblasts (Fig. 4).

**Effect of periostin and tenascin C treatment on the gene expression of MMPs and TIMPs in nasal polyp-derived primary epithelial cells ex vivo**

As epithelial cells are a source of MMPs and TIMPs, we next observed the regulation by ECM proteins of the expression of those MMPs and TIMPs in nasal polyp-derived epithelial cells. Contrary to the results in the fibroblasts, periostin treatment in the epithelial cells had almost no effect on the expression of those MMPs and TIMPs, except for the up-regulation of MMP-7 at higher dose treatment (Fig. 5); while tenascin C treatment significantly increased the expression of MMP-3, MMP-8 and MMP-9 (Fig. 6).

**Discussion**

Tissue remodeling is a cardinal CRSwNP pathogenesis, which is a dynamic process of ECM formation and degradation, leading to changes in tissue architecture. MMPs are key enzymes with proteolytic activities that can degrade various ECM components and can lead to progressive histologic changes. Presently, abundant evidence indicates that CRSwNP undergo up-regulated alterations of MMPs[4, 5, 11]. Anti-MMP treatment has been shown to modify polyp size and improve postoperative healing outcome. [23] Therefore, MMPs are associated with the formation of nasal polyps. Further investigation is needed of the mechanism by which MMPs are stimulated in polyp tissues. In this context, our results helped to address the knowledge gap by analyzing the correlation of ECM proteins with MMPs and TIMPs in patients, and by ex vivo experiments. We identified that there is a positive correlation of periostin and tenascin C with MMPs and found that periostin and tenascin C could stimulate the ex vivo expression of MMPs mainly in different cells, periostin in fibroblasts and tenascin C in epithelial cells.

Previous studies provided evidence for higher levels of MMP-2, MMP-3, MMP-7, MMP-8, and MMP-9 in nasal polyps.[5, 11, 12] Correspondingly, we found that MMP-3, MMP-7, MMP-8 and MMP-9 were increased in CRSwNPs compared with controls, and MMP-8 and MMP-9 were increased in CRSwNPs compared with CRSsNP. We failed to observe a difference in MMPs between CRSsNP and the controls. Our results verified the roles of MMPs in the pathogenesis in CRSwNP patients, but not in CRSsNP patients. We also found higher levels of periostin in nasal polyps compared with the controls and higher levels of tenascin C in nasal polyps compared with CRSsNP and the controls. Thus we investigated whether there exists a relationship between the two ECM proteins and MMPs. The results showed that the
ECM proteins were positively related to MMP-2, MMP-3, MMP-7, MMP-8 and MMP-9. Periostin and tenascin C have been reported to stimulate the expression of MMPs beyond nasal polyps.[13, 14, 24] In this context, we speculated that periostin and tenascin C might be able to regulate the expression of these MMPs within nasal polyps.

Fibroblasts and the nasal epithelium are both sources of MMPs in NPs,[17, 25] the imbalanced regulation of which might contribute to the pathogenesis of CRSwNP. Thus we investigated the role of periostin and tenascin C in promoting the expression of MMPs via fibroblasts and the nasal epithelium in nasal polyps. Our results demonstrated that periostin could stimulate the expression of MMPs via fibroblasts, while tenascin C worked mainly via epithelial cells. The up-regulated MMPs stimulated by periostin and tenascin C, were in correspondence with the MMPs that showed significantly higher levels in tissue homogenates of CRSwNP. The ex vivo findings suggest that periostin and tenascin C may contribute to the formation of NPs via regulating the expression of MMPs in different cells.

Previous studies have found evidence that periostin can stimulate the expression of MMPs. For instance, Mukundan et al.[13] found that periostin induced the expression of MMP-13 in cartilage and Hakuno et al. [14] revealed that periostin could promote the levels of MMP-2 and MMP-13 from valvular interstitial cells, and could increase the expression of MMP-2 and MMP-9 in macrophages in vitro. However, within nasal polyps, if and how periostin induces the expression of MMPs is still unknown. We showed that periostin induced the expression of MMP-2, MMP-3, MMP-7 and MMP-9 in nasal fibroblasts and the expression of MMP-7 in nasal epithelial cells. Periostin has been confirmed as a novel biomarker for the formation of nasal polyps,[10] whereas MMPs are involved in tissue remodeling, thus contributing to the formation of nasal polyps. Higher levels of MMP-9 indicated an unfavorable outcome of CRSwNPs after endoscopic sinus surgery (ESS). [26, 27] In this study, we found higher levels of MMP-9 in CRSwNP versus CRSsNP and identified that periostin induced the expression of MMP-9 in fibroblasts. It suggested that periostin might be able to mediate, at least in part, the pathogenesis of CRSwNP via regulating the production of MMP-9 in nasal fibroblasts.

Tenascin C, as an ECM protein, could be increased in parallel with MMPs in some pathological states.[15] However, the regulatory role of tenascin C on MMPs in nasal polyps remains unknown. In the present study, we found that tenascin C induced the expression of MMP-3, MMP-8, and MMP-9 in the nasal epithelium, but not in fibroblasts. There is substantial evidence that tenascin C contributes to tissue remodeling via the upregulation of MMP-9 in the mouse model of the cardiovascular system (e.g., cardiac remodeling, hepatic ischemia/reperfusion, subarachnoid hemorrhage, etc.).[15, 24, 28, 29] and tenascin C is capable of inducing the expression of MMP-9 in breast cancer cells and isolated neutrophils.[24, 30] Recently, Kanagala et al.[31] found higher levels of plasma MMP-8 in heart failure patients with tenascin C above the median plasma concentration than in those with tenascin C below the median plasma concentration. Consistent with this, we found a positive correlation of tenascin C with MMP-8 in nasal tissue homogenates in this study and observed that tenascin C could dramatically promote the expression of MMP-8 in nasal polyp epithelial cells, indicating the tenascin C might be the main factor driving the expression of MMP-8. Recently, the pro-inflammatory role of MMP-8 via isolated macrophages
was identified in mice. Our data addresses the knowledge gap and suggests that besides tissue remodeling, tenascin C has the potential to enhance the inflammation within nasal polyps. This hypothesis needs to be further examined in the future.

To our knowledge, this is the first study to describe the role of periostin and tenascin C in regulating the expression of MMPs in NP. The degradation of ECM in polyp tissues induced by MMPs is a risk factor for the morbidity of CRSwNP. In addition, the mechanisms by which MMPs are synthesized need to be further investigated. We revealed that fibroblasts and the nasal epithelium are both sources of MMPs within nasal polyps. TIMP-1 might be able to reduce the effects of the expression of MMP-9, however, the levels of MMP-9 and TIMP-1 were negatively correlated with disease severity in CRS. Although higher levels of TIMP-1 and TIMP-2 were found in CRSwNPs, we failed to verify the regulatory roles of periostin and tenascin C on TIMPs. In this regard, further studies are required to illuminate how TIMPs are induced in nasal polyps. It has been known that CRSwNP patients prominently manifest eosinophilic inflammation and periostin has been reported to have a role in orchestrating eosinophil infiltration. Our data provide new insight into the role of periostin in the pathogenesis of CRSwNP, which promotes tissue remodeling via MMP production by fibroblasts during inflammation. Additionally, tenascin C contributes to tissue remodeling in a different manner. Tenascin C stimulates the production of MMPs mainly in the nasal epithelium, not in fibroblasts, and it mainly stimulates the production of MMP-8. Among the up-regulated MMPs in this study, MMP-9 is extensively confirmed to be increased in NPs. We showed that periostin and tenascin C are both able to stimulate the expression of MMP-9 via fibroblasts and the nasal epithelium. There are several limitations to our study. First, the assessment of the tissue remodeling molecules was based only on the mRNA expression, which needs to be verified according to the levels of corresponding proteins in NP tissues. Second, the number of cases involved in the ex vivo experiments is small. Finally, we failed to investigate the regulatory role of periostin and tenascin C on patients with different endotypes, including eosinophilic and non-eosinophilic CRSwNPs, which need further investigation.

Conclusions

Our study showed the correlation of periostin and tenascin C with some members of the MMP family, which were confirmed to be increased in patients with CRSwNP and identify that both periostin and tenascin C have regulatory roles in the expression of these MMP, acting on different types of cells, mainly fibroblasts for periostin and nasal epithelium for tenascin C. We provide evidence for the pathogenic roles of periostin and tenascin C in the formation of nasal polyps. Our findings have the potential to identify key factors enhancing tissue remodeling, which will be necessary to further uncover the pathogenesis of CRSwNPs.

Abbreviations

BEGM: bronchial epithelial growth medium; CRSsNP: chronic rhinosinusitis without nasal polyposis; CRSwNP: chronic rhinosinusitis with nasal polyposis; ESS: endoscopic sinus surgery; ECM: extracellular matrix; MMP: matrix metalloproteinase; NP: nasal polyps; TIMP: tissue inhibitor of metalloproteinase
matrix; FBS: fetal bovine serum; MMPs: Matrix metalloproteinases; NPs: nasal polyps; PBS: phosphate-buffered saline; PCR: polymerase chain reaction; TIMPs: tissue inhibitors of metalloproteinase

Declarations

Ethics approval and consent to participate:

The study protocol was approved by the Ethics Committee of Beijing Tongren Hospital, and informed consent forms were obtained from all of the enrolled patients.

Consent for publication:

Not applicable

Availability of data and materials:

The data generated and analysed during the current study are not publicly available due to individual privacy but are available from the corresponding author on reasonable request.

Competing interests:

No author has any competing interests to declare.

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Authors' contributions:

M.W. and K.D. conceived and designed the experiments. K.D. and M.W. wrote the manuscript. K.D., M.W., P.W., P.Y., and Y.L performed the experiments. N.Z., X.D.W., L.Z., and C.B revised the manuscript.

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