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Tissue remodelling in chronic rhinosinusitis – review of literature

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ABSTRACT: CRS is a process involving a number of adverse changes in the mucosa of the paranasal sinuses and nasal polyps, e.g. increased fibroblast proliferation, angiogenesis, increased formation of fibrous tissue (subepithelial fibrosis) and tissue destruction. There are biomarkers whose levels can be increased in chronic inflammation of the paranasal sinuses: peripheral blood eosinophilia, IgE immunoglobulin, cytokines – IL-4, IL-5, IL-13, IL-25, IL-33, periostin, P-glycoprotein, CXCL-12, CXCL-13, INF-Ɣ, TNFα, TGFβ1, albumins, eotaxin. These biomarkers are not pathognomonic for CRS. The concentration of biomarkers is also increased in bronchial asthma and atopic dermatitis. The TGFβ, in particular the β1 subunit, was identified as the main factor involved in the remodelling of tissue stroma. In conjunction with continuous improvement of tissue testing methods, it is advisable to search for new factors that will more accurately allow the assessment of tissue remodelling in the chronic processes of paranasal sinuses.

KEYWORDS: chronic rhinosinusitis, nasal polyps, tissue remodeling

ABBREVIATIONS

CRS – chronic rhinosinusitis
CRSsNP – chronic sinusitis without nasal polyps
CRSwNP – chronic sinusitis without nasal polyps
ECP – eosinophil cationic protein
ESS – endoscopic sinus surgery
FGF – fibroblast growth factor
MAPKs – mitogen-activated protein kinases
MMPs – matrix metalloproteinases
NPDF – nasal polyp-derived fibroblasts
TGFβ1 – transforming growth factor beta-1
TIMPs – tissue inhibitor of metalloproteinases
VEGF – vascular endothelial growth factor

INTRODUCTION

According to European Guidelines, chronic rhinosinusitis, or CRS (EPOS 2012) was defined as the occurrence of two symptoms lasting more than 12 weeks of which one is nasal congestion and/or anterior or posterior nasal drip, which may also be accompanied by pain, a sensation of distension of facial skeleton and/or cough. There are two main types of chronic sinusitis – with and without nasal polyps (CRSwNP and CRSsNP, respectively) [1]. In the pathophysiology of chronic sinusitis, three main groups are dependent on the immune response – Th1-dependent, Th2-dependent and Th17-dependent. Th-1 dependent (humoral) response is associated with CRSsNP, neutrophilia, elevated levels of myeloperoxidases, interferon gamma (IFN-Ɣ), interleukin IL-2 and tumour necrosis factor (TNF-α). Chronic rhinosinusitis – usually associated with a Th-2 dependent cellular response – which is characterised by eosinophilia, elevated levels of IL-2, IL-5, IL-10, IL-13, and ECP (eosinophil cationic protein). Th17-dependent cellular response is predominant in inhabitants from Asia and mainly associated with chronic sinusitis with polyps. Th17 response mainly shows increased expression of cytokines: IL-6, IL-17, IL-22 and tumour necrosis factor TNFα [7, 17, 18, 23].

TISSUE REMODELLING IN CHRONIC SINUSITIS

Tissue remodelling is a dynamic process that results in a temporary or permanent change in the histological composition of tissues. This process may occur with the production or degeneration of the extracellular matrix – this results in the formation of normal and/or pathological tissue [2]. The main histological features of tissue remodelling are macrophages and lymphocyte migration, fibroblast proliferation, angiogenesis, subepithelial fibrosis and tissue degeneration. There are many studies showings that tissue remodelling also occurs in chronic sinusitis, and the features of stromal remodelling vary depending on the type of inflammation [4].

Typical tissue remodelling in CRSwNP is characterised by the formation of pseudocysts, oedema, accumulation of albumin, reduction in collagen content in the extracellular matrix and reduced expression of TGF β1. However, chronic sinusitis without polyps is found to display an elevation in IFN-Ɣ, TGF β1 and an increase

in collagen content in the extracellular matrix [5]. Due to the complexity and variety of mechanisms of the inflammatory process in stroma of the nasal polyp, we can find numerous research results in the literature regarding biomarkers of chronic inflammatory process in the paranasal sinuses and nasal polyps [6].

Workman et al. published a list of biomarkers whose concentration is elevated in chronic inflammation of the paranasal sinuses. These biomarkers are not limited to CRS – they can be found in bronchial asthma and atopic dermatitis. Material for biomarker assessment can be obtained from peripheral blood, nasal secretions and tissue of nasal polyp. The list of biomarkers includes, among others: peripheral blood eosinophilia, IgE immunoglobulin, cytokines – IL-4, IL-5, IL-13, IL-25, IL-33, periostin, P-glycoprotein, CXCL-12, CXCL-13, extracellular matrix metalloproteinases [6]. Other publications also specify INF-ϒ, TNFα, TGFβ1, albumin content, eotaxin [7].

The phenomenon of tissue remodelling was first described in the lower respiratory tract in the course of bronchial asthma [3]. Airway tissue remodelling involves a number of adverse changes, including exfoliation of bronchial epithelium, subepithelial fibrosis, goblet cell hyperplasia, hypertrophy of bronchial myocyte, submucosal angiogenesis and increased extracellular matrix deposition [3].

TGFβ – a cytokine with many functions in organisms – controls cell growth, cell proliferation, differentiation and apoptosis. Some studies specify TGFβ-1 as the main factor involved in tissue remodelling in chronic sinusitis, mainly by induction of procollagen synthesis, whose increased deposition causes subepithelial fibrosis. It has been shown that the main source of TGFβ in nasal polyps is eosinophil infiltrates. Increased expression of TGFβ exacerbates stromal fibrosis, visible in the process of nasal polyp formation, mainly due to the increased secretion of collagen and fibronectin in the extracellular matrix.

Some authors suggest that the proliferation of fibroblasts in nasal polyps may be dependent on the concentration of TGFβ1 – a reduced concentration stimulates the proliferation process, while an increased concentration inhibits it [5, 9, 10]. On the other hand, other authors propose the opposite tendency – some studies have demonstrated elevated levels of TGFβ1 in nasal secretion in patients with CRSwNP compared to the control group and with CRSsNP.

TGFβ also affects the imbalance between intracellular MMPs and TIMPs.. The literature mainly lists elevated concentrations – MMP-1 (collagenase), MMP-2, MMP-9 – gelatinase and MMP-13 [11]. Watlet et al. report that the increase in concentration of neutrophil MMP-9 has a negative impact on the patient's quality of life and increases time of healing/regeneration of tissues after endoscopic sinus surgery [20].

Brescia et al. demonstrated that tissue remodelling is a dynamic process with differences in the number of tissue eosinophilia between primary and recurrent CRSwNP. Histopathologically tissue collected during primary surgery and at 3, 6 and 12 months after the first ESS treatment was examined (recurrence was found in 7 out of 32 patients). Studies have shown a positive correlation between all examined histopathological parameters and tissue eosinophils and the number of eosinophils in peripheral blood. Revision surgery found a positive correlation of only the thickness of the basement membrane with tissue eosinophilia and goblet cell hyperplasia. In recurrent CRSwNP, there was a positive correlation between tissue eosinophilia and peripheral blood eosinophils, but the average number of tissue eosinophils was significantly lower than at the time of primary surgery [19].

Angiogenesis – this process is mainly due to growth factors – primarily VEGF and FGF – these factors directly stimulate this process. VEGF is a dimeric heparin binding glycoprotein with a molecular weight of approx. 45kD, synthesised mainly by epithelial cells and inflammatory cells. The synthesis of this cytokine is also stimulated by other growth factors, including TGFβ1. VEGF induces endothelial cell proliferation and increases vascular permeability; it also participates in wound healing and in chronic inflammation. The expression of angiogenic growth factor was assessed – it was shown that the expression of VEGF is higher in nasal polyp cells compared to the expression found in the nasal mucosa (material taken from the nasal mucosa) [21, 22]. Subepithelial fibrosis is the result of the deposition of improperly formed collagen fibres (including type I, III, V), fibronectin, tenascin and accumulation of extracellular matrix components within the basement membrane [8].

The process of early development of nasal polyps includes the diversification of fibroblasts and myofibroblasts whose activity can be expressed by alpha-SMA expression and overproduction of extracellular matrix components – one of the proteins of matrix is periostin, produced mainly by fibroblasts, which affects the process of tissue remodelling in the respiratory tract by induction of Th2-dependent response. Periostin affects myofibroblast differentiation, among others by inducing it via interleukins: IL-4 and IL-13. The presence of periostin has been demonstrated in the mucosa of the paranasal sinuses, nasal polyps, lower respiratory tract and myocardium [14, 15].

In a study conducted by A. Z. Maxfield et al. serum periostin levels have been shown to be higher in patients with CRSwNP compared to patients with CRSsNP and control patients. Yet no proof was found of a positive correlation with nicotinism, gender, use of oral steroid treatment in the past month, use of nasal steroids, previous rhinological interventions or hypersensitivity to acetylsalicylic acid [16].

The process of remodelling of nasal polyp tissues is affected by interleukin 25 (IL-25), a cytokine produced by Th2 lymphocytes, stimulating them to increased production of eosinophils by secreting IL-4, IL-5 and IL-13. IL-25 expression has been shown to be significantly elevated in nasal polyps in patients with CRSwNP than in patients with CRSsNP [13]. The effects of IL-25 on myofibroblast differentiation, extracellular matrix composition and expression of MMP matrix in nasal polyp-derived fibroblasts, or NPDFs were studied. IL-25 induced release of α-SMA, fibronectin, collagen from NPDF has been shown to be associated with activation of mitogen-activated protein kinase (MAPK) and NF-κib [24].

CONCLUSION

Tissue remodelling is a dynamic process. Its course is probably influenced by comorbidities, used pharmacotherapy and previous surgical procedures. Despite constantly improving tissue testing techniques and numerous studies, no pathognomonic factor that can characterise chronic sinusitis has been demonstrated to date. Therefore, new factors are being sought that will more accurately enable the assessment of tissue remodelling in disease processes both in the postoperative course and during healing in chronic sinusitis.

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