Title of dissertation:

Chronic rhinosinusitis – an attempt to identify new disease biomarkers

Abstract

Chronic rhinosinusitis (CRS) affects almost 5 - 12% of the global population. CRS appears in the two main endotypes: chronic rhinosinusitis with nasal polyps (CRSwNP) and without (CRSsNP). The symptoms of CRS include at least two of the following: nasal blockage/ obstruction/ congestion or nasal discharge (anterior / posterior nasal drip), facial pain/ pressure, reduction/ loss of smell due to time no less than 12 weeks. CRS relates to chronic inflammation and nasal airway epithelium remodeling. Factors contributing and leading to exacerbation of disease include bacterial, viral, fungal infections, airway pollution, as well as comorbidity diseases such as: allergy, cystic fibrosis, anatomical dysfunctions or immunosuppression. Despite the fact that CRS occurs commonly and significantly reduces the quality of life, the molecular background of disease remains elusive. The better understanding of CRS etiopathogenesis might lead to identification of the novel biomarkers as well as diagnostic and therapeutic solutions.

The key aspects of CRS pathogenesis include: altered immunity activity and structural with functional changes in the upper airway epithelium. It triggers to obstruction of the paranasal sinuses opening and in consequence symptoms of disease. In our article: "*Immunological Aspects of Chronic Rhinosinusitis"* the literature review concerning modification of respective immune cells populations and disabilities in the paranasal sinuses mucosa has been done.

Due to the fact that the newest scientific reports indicate the crucial role of small extracellular vesicles, called also exosomes, in the pathogenesis of various diseases, the aim of the our next article *„The Emerging Role of Small Extracellular Vesicles in Inflammatory Airway Diseases"* was to review the literature concerning the role of exosomes in the pathogenesis of chronic upper inflammatory diseases with special focus on chronic rhinosinusitis. In this article the exosomes biogenesis, transported molecular cargo their functions as well as diagnostic and therapeutic potential has been described.

Current scientific reports describe that exosomes transport molecular cargo reflecting the activity of originated cell. In case of CRS, it has been found that epithelium secrete the

exosomes with the content involved in the disease pathogenesis. The key aspects of CRS pathogenesis are tissue remodeling with loss of its physiological functions and altered activity of residue in the subepithelial area nasal fibroblasts. It has been found that TGFβ1/Smad that is involved in the tissue remodeling in various diseases is active also in case of CRS. However, in case of CRS, the activity of TGFβ1/Smad signaling in proper disease endotype remain inconclusive. Another studies, concern the role of adenosine and cAMP – related pathways in the CRS pathogenesis of upper chronic inflammatory pathways. What is more, the relationship between TGFβ and adenosine in the altered fibroblast's function. Adenosine might occur due to 2',3'- cAMP conversion that is previously derived from mRNA breakdown. In this process takes part CNPase – the enzyme converting the 2',3'- cAMP to 2'-AMP and 3'-AMP. The aim of our study was the evaluation of the sinus epithelium expression of TGFβ1, Smad2, pSmad3 oraz CNPase derived from CRSwNP, CRSsNP and control group patients. Our immunohistochemistry staining analysis indicated the positive expression for all of them in each group, however the level of expression was different between proper groups. The level of Smad2 expression was higher in case of CRSsNP comparing to CRSwNP and controls, pSmad3 and TGFβ1 were higher in CRSwNP than in controls and CNPase was decreased in CRSsNP in compared to controls. In addition, positive correlation between CNPase and TGFβ1 in CRSsNP has been found and it suggest their possible collaboration. The expression of TGFβ1, Smad2, pSmad3 were positively correlated also with selected clinical symptoms. Our study has been described in detail in the article: „*Evaluation of CNPase and TGFβ1/Smad Signalling Pathway Molecule Expression in Sinus Epithelial Tissues of Patients with Chronic Rhinosinusitis with (CRSwNP) and without Nasal Polyps (CRSsNP)"*.

In summary, the study conducted as the part of doctoral thesis indicated the differences in the sinus's epithelium expression of TGFβ1, Smad2, pSmad3 oraz CNPase between CRSwNP, CRSsNP and control patients. Importantly, we as the first has been shown the CNPase expression in the upper airway epithelium of CRS patients and its possible cooperation with TGFβ1. Moreover, CNPase might regulate exosomes concentration that as we have described in our review article, play crucial role in modulation of immune and mucosal cells activity. The research performed in the doctoral thesis might open new horizons to discover novel mechanisms involved in the CRS pathogenesis, specific endotype's biomarkers and more effective diagnostic and therapeutic solutions in the future.