

lek. Katarzyna Mycroft-Rzeszotarska

Streszczenie w języku angielskim

The analysis of transcriptional profiles and phenotypes of eosinophils in the blood and in the airways in COPD patients

Chronic obstructive pulmonary disease (COPD) affects approximately 10% of the world's population aged 30-79. In developed countries, the main factor involved in the pathogenesis of the disease is cigarette smoking. Repeated exposure to toxic factors in inhaled air contributes to the development of chronic inflammation in the respiratory tract, destruction of the lung parenchyma and structural changes in the walls of small pulmonary vessels. COPD is progressive and irreversible, and late diagnosis and difficulties in treatment make it the third cause of death in the world according to the estimates by the World Health Organization.

Hence, in recent years, many efforts have been made in the search for biomarkers that would enable the selection of COPD patients who could benefit from a personalized form of treatment. One of the biomarkers extensively studied in COPD is the number of eosinophils in peripheral blood. Despite many efforts, the role of eosinophils in the pathogenesis and treatment of COPD remains ambiguous.

This doctoral dissertation consists of three research papers published in peer-reviewed journals: 1 review and 2 original papers. The introduction to the doctoral dissertation is based on the review of the world literature (Eosinophils in COPD-Current Concepts and Clinical Implications, doi: 10.1016/j.jaip.2020.03.017). The paper presents the mechanisms associated with the development of eosinophilic inflammation in the respiratory tract in COPD and discusses the possible impact of this type of inflammation on the course of the disease. Moreover, the available literature on the number of eosinophils in peripheral blood as a biomarker was analyzed. The association between the number of eosinophils in peripheral blood and the number of eosinophils in the respiratory tract is equivocal and the number of eosinophils in the blood itself was not found to be a stable parameter. However, a relationship between the response to corticosteroids and the number of eosinophils in the blood in patients with exacerbations has been found.

In both original papers a comparative analysis of eosinophils in patients with COPD and asthma was performed. In the study Blood and Sputum Eosinophils of COPD Patients Are Differently Polarized than in Asthma (doi: 10.3390/cells12121631), we evaluated the

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expression of several surface molecules on eosinophils using flow cytometry, and then compared it to eosinophils in peripheral blood and in the respiratory tract (induced sputum). We observed that eosinophils in the blood exhibited increased expression of CD125, CD193, CD62L, and CD14 compared to eosinophils in induced sputum in the COPD, asthma, and control groups, which might suggest a change in eosinophil phenotype after recruitment to the respiratory tract regardless of diagnosis.

In the group of COPD patients, a higher percentage of CD193+ and CD66b+ eosinophils was observed in induced sputum compared to the control group, and a higher percentage of CD11b+ eosinophils compared to the asthma group. Subsequently, eosinophil subpopulations were characterized by the expression of the pair of markers CD125 and CD193. In all three groups, eosinophils in blood and sputum were predominantly CD193+CD125+. A decreased level of

CD193-CD125+ eosinophils was found in sputum in COPD patients compared to the control group. Our study results suggest different polarization of tissue and systemic eosinophils and differences in eosinophil subpopulations in COPD patients compared to those with asthma or healthy individuals.

No correlation was found between the expression of CD125 on eosinophils in sputum or blood and the concentration of IL-5 in sputum, nor between the expression of CD193 on eosinophils in sputum or blood and the concentration of eotaxin-3 in sputum. Furthermore, in none of the studied groups was found a correlation between IL-5 or eotaxin-3 and the percentage of CD125+CD193+ eosinophil subpopulations.

In the study Transcriptional profiles of peripheral eosinophils in chronic obstructive pulmonary disease and asthma – an exploratory study (doi: 10.1111/jcmm.70110) we assessed and compared transcriptional profiles of eosinophils in peripheral blood in patients with COPD and asthma. The RNA-Seq data analysis identified 26 differentially expressed genes in COPD and asthma. The most strongly up-regulated genes in COPD were CCL3L1 and CCL4L2, which encode chemokines. The CCL3L1 gene encodes macrophage inflammatory protein 1 α (MIP-1 α). MIP-1 α -CCR5 binding is linked to the processes associated with tight junction injury in the airway epithelium in COPD. CCR5 also serves as a receptor for MIP-1 β encoded by i.a. CCL4L2 which in our study was found to be up-regulated in COPD patients. Both MIP-1 α and MIP-1 β are monocyte and macrophage chemoattractants. The upregulated mRNA expression of CCL3L1 in COPD eosinophils

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observed in our study may suggest that in COPD eosinophils attract macrophages into the lungs rather than drive local eosinophilic inflammation. This finding underscores the different function of eosinophils in asthma and COPD pathobiology and might explain different ICS-sensitivity of patients with COPD and asthma.