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Wpływ pyłu zawieszonego w powietrzu na nabłonek oddechowy w interakcjach pomiędzy nabłonkiem, komórkami dendrytycznymi i makrofagami w obturacyjnych chorobach płuc

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych

Warszawskiego Uniwersytetu Medycznego

Warszawa 2022

3. Streszczenie w j. angielskim

The impact of airborne particulate matter on respiratory epithelium in the interactions between epithelium, dendritic cells and macrophages in obstructive lung diseases

Environmental pollution, such as elevated concentrations of airborne particulate matter (PM), is an important element affecting public health. The physiological organisation of the epithelium plays a key role in the formation of the airway barrier. Interactions of structural cells with immune cells residing in the airways (macrophages and dendritic cells), initiate a local immune response. Asthma and chronic obstructive pulmonary disease (COPD) are among the most common chronic respiratory diseases, which are characterised by an increased influx of immune cells into the lungs during inflammatory response. In consequence, this process leads to an increased release of mediators at the site of inflammation, activation of local repair mechanisms, epithelial remodelling, epithelial function impairment and increased mucous secretion. Chronic inflammation in the airways contributes to the symptoms of the disease, including dyspnoea (at rest or during exercise), coughing or reduced lung function.

Particulate matter with an aerodynamic diameter up to 10 μm, (PM_{10}) is a mixture of particles of the $PM_{2.5}$ fraction, with an aerodynamic diameter up to 2.5 μm, and additional, larger, and more diverse components. Therefore, it is characterised by a different chemical composition and toxic effects from the isolated $PM_{2.5}$ fraction. The most important mechanisms of PM_{10} negative action on the airway epithelium include modulation of innate immunity, the inflammatory response and induction of oxidative stress, which course and intensity depends on the chemical composition of the ambient air pollution. Exposure to air pollutants, including PM_{10}, shows negative local effects on the respiratory epithelium, modulates intercellular interactions and impairs the organism's defence capabilities, which in turn can lead to exacerbations and progression of obstructive lung diseases.

The research conducted in the present study was aimed to determine the changes occurring in the nasal epithelium in response to stimulation by PM_{10} collected from urban areas. The analysis was carried out at the molecular, biochemical and structural level, the epithelial cells used in the study were collected from asthma patients, COPD patients and healthy individuals. The following objectives of the study were formed (1) a review of the world literature characterizing the effects of PM_{10} on airway epithelial physiology

in asthma and COPD, (2) analysis and comparison of the effects of PM_{10} exposure on the inflammatory response of nasal epithelium from patients with asthma or COPD and healthy subjects using a mono- and co-culture *in vitro* model, (3) determination of airway epithelial integrity and expression of remodelling markers in response to PM_{10} stimulation in the epithelium of healthy subjects, asthma or COPD patients, (4) transcriptomic analysis of the response of nasal epithelium from patients with obstructive lung diseases and healthy subjects co-cultured with macrophages and dendritic cells after exposure to PM_{10}.

The methodology of the study included the recruitment of asthma, COPD patients and healthy volunteers, isolation of nasal epithelial cells obtained from nasal mucosa brushing, isolation and specialisation of macrophages and dendritic cells from peripheral blood monocytes. The study used co-cultures in which cells from the donor (macrophages, epithelium, dendritic cells) consisted as an individual experimental model. Cultures were exposed for 24 hours to PM_{10} at a concentration of 100 μg/ml. Epithelial cells cultured at the air-liquid interface (ALI) consisted of multiple types of specialised epithelial cells, including basal, ciliated, and secretory cells. Dendritic cells (moDC) and macrophages (moMφ) derived from peripheral blood monocytes were used as a model of immune cells recruited into the airways. The research model used in experiments assessed the effects of PM_{10} on the airway epithelium, taking into account the influence of simple intercellular interactions that modulate the tissue immune response. In addition, the use of large-scale methods of analysis, i.e., transcriptome analysis, estimated a comprehensive assessment of the diverse mechanisms responsible for pathophysiological processes following exposure to air pollutants in obstructive lung diseases. The results of the experiments and analyses are presented in the form of published articles that constitute the individual chapters of the dissertation.

A review of the world literature allowed for a broad analysis of published research findings on the negative effects of PM_{10} fraction and its significant impact on disease onset and symptom exacerbations among patients with asthma and COPD. The most relevant results of our own research indicated that the airway epithelium of people with obstructive lung disease, COPD patients in particular, has the strongest pro-inflammatory response after exposure to PM_{10}. Stimulation with PM_{10} increased IL-6 and IL-8 expression in epithelium co-cultured with dendritic cells and macrophages compared to epithelial monocultures, indicating an important role for recruited cells in the local airway inflammatory response. 24h exposure to PM_{10} did not alter

the integrity of intercellular junctions in the epithelium in all analysed groups but affected EGFR and ST2 expression on the asthmatic epithelium. The results of transcriptomic analysis of airway epithelium showed the distinct nature of the local biological response in obstructive lung diseases after exposure to urban particulate matter compared to healthy subjects. In the applied *in vitro* model, PM_{10} stimulation among subjects with obstructive lung diseases increased mRNA expression of genes responsible for the immune response, particularly leukocyte influx, additionally, in asthma, it increased mRNA expression of genes related to structural cells remodelling processes, while in COPD it modulated the oxidative stress response. In healthy subjects, exposure to PM_{10} activated pathways associated with regenerative processes in epithelial cells.