Mechanisms of inflammatory signalling in chronic lung diseases

Transcriptomics & metabolomics approaches

av
Bettina Levänen
BSc

Huvudhandledare:
Åsa Wheelock
Karolinska Institutet
Inst f Medicin
Enheten för Lungmedicin

Bihandledare:
Professor Johan Grunewald
Karolinska Institutet
Inst f Medicin
Enheten för Lungmedicin

Docent Magnus Nord
Karolinska Institutet
Inst f Medicin
Enheten för Lungmedicin

Fakultetsopponent:
Professor Guy Brusselle
Ghent University Hospital, Belgium
Faculty of Medicine

Betygsnämnd:
Docent Marie Carlson
Akademiska Sjukhuset, Uppsala
Inst f Medicinska vetenskaper
Sektionen för Gastroenterologi & Hepatologi

Docent Andor Pivarcsi
Karolinska Institutet
Inst f Medicin
Enheten för dermatologi & venereologi

Docent Mikael Adner
Karolinska Institutet
Inst f Miljömedicin (IMM)
Enh f experimentell astma & allergiforskning

ABSTRACT

Sarcoidosis, asthma and chronic obstructive pulmonary disease (COPD) are inflammatory pulmonary diseases with many different clinical phenotypes. A central characteristic of all three diseases is the altered airway function due to inflammation. In sarcoidosis this is believed to be caused by a yet unidentified substance(s), in COPD largely by exposure to inhaled toxicants, e.g. smoking and in asthma due to an excessive reaction to an often harmless environmental substance. Long-term inflammation may cause tissue damage and in some cases irreversible destruction and remodelling. The current absence of a cure for these diseases points out a need to define the pathologic mechanisms in order to personalise treatment.

In this dissertation we investigated the above mentioned diseases using global screening methods in combination with validation techniques. We investigated intracellular wingless/integrated (WNT)-signalling in bronchoalveolar lavage (BAL) and epithelial cells in sarcoidosis. Oxylipin–levels were measured in BAL fluid of asthmatics. And global screening for miRNA and mRNA expression in pulmonary inflammatory cells in COPD, as well as miRNA in extracellular exosomes from both asthmatics and COPD patients, were performed.

WNTs are lipoglycoproteins, important in several cellular functions such as proliferation and differentiation, which by binding to membrane receptors starts an intrecellular signalling cascade involving β-catenin. The results revealed clear differences in *WNT* expression levels in sarcoidosis patients, suggesting a role for the molecules in the development of fibrosis. Oxylipins are lipids synthesised on demand from omega-3 and omega-6 unsaturated fatty acids and involved in various inflammatory processes. Differing oxylipin levels in BAL fluids of mild asthmatics were detected in response to subway air exposure, indicating a decreased protective response to noxious stimuli in individuals with lowered lung function. Exosomes are nanosised vesicles, created in the multivesicular endosomes in various cells, believed to be involved in the extracellular transport of molecules. MikroRNA (miRNA), shown to be present in exosomes, are small RNAs capable of affecting translation of proteins through the regulation of mRNA. Expression of miRNAs in both cells and exosomes and geneexpression in the BAL cells were significantly different between smoking COPD patients and healthy smokers. These combined results clearly indicates global changes in different signalling cascades and pathways, requiring global analysis of expression on multiple levels in order to elucidate mechanistic differences between the diseases.

The projects included in this dissertation are part of larger studies. In further studies we aim to integrate the results from several platforms; transcriptomics, proteomics and metabolomics with complex analysis methods in order to elucidate the similarities, and more importantly, the differences between these pulmonary diseases. By doing this we will acquire a better understanding of the pathological reasons and further our understanding of these inflammatory pulmonary diseases. This may ultimately lead to earlier and more specific diagnostic tools, and to the development of better and more personal treatment options for the patients.