Universität Basel

Research Project

Towards precision medicine in COPD-Investigation of glucocorticoid responsiveness using primary airway cells from COPD patients

Third-party funded project

Project title Towards precision medicine in COPD-Investigation of glucocorticoid responsiveness using primary airway cells from COPD patients
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Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease and, currently, a leading cause of chronic morbidity and mortality. Although inhaled corticosteroids (ICS) are highly effective in asthma, their effect in COPD is highly differentiated among patients. Thus, misuse of ICS in an unidentified population of COPD patients that do not respond to ICS results in serious side effects and economic burden. It is imperative therefore, to elucidate the mechanisms involved in ICS responsiveness in COPD. We are currently evaluating the responsiveness to ICS in a cohort of 188 COPD patients that participate in the HISTORIC study, an investigator-initiated and driven, controlled study in the Clinic of Pneumology, University Hospital Basel. Aim of the current proposal: To investigate cellular and molecular parameters associated with glucocorticoid responsiveness in COPD patients, using primary airway cells, established from endobronchial biopsies of the 188 COPD patients who participate in the HISTORIC study.Objectives: COPD patients (n=188) will be divided into “responders” and “no-responders” to ICS treatment. In each group we will: 1) establish airway smooth muscle cells (ASMC), bronchial epithelial cells (BEC) and fibroblasts from endobronchial biopsies; 2) assess the expression of glucocorticoid receptor (GR) isoforms, GRa and GRß in tissue sections of the airways, as well as in primary airway cells; 3) evaluate the activation of GR receptor in response to glucocorticoids in primary ASMC, BEC and fibroblasts; 4) study the expression, activation and nuclear binding of GR-interacting transcription factors, such as activator protein-1 (AP-1), nuclear factor kB (NF-kB) and cAMP response element-binding protein (CREB), for their possible role in glucocorticoid unresponsiveness, in primary airway cells; 5) study gene and protein expression as well as the activity of histone deacetylase (HDAC) in primary airway cells and 6) characterize GR-regulated cellular signaling cascades. Methods: Primary ASMC, BEC and fibroblasts will be established from endobronchial biopsies from 188 patients included in the HISTORIC study. Activation of the GR in these cells will be assessed by translocation of the GR from the cytoplasm to the nucleus and by studying GR phosphorylation, ubiquitination, acetylation and methylation in the presence and absence of glucocorticoids. The expression of GRa/GRß , HDAC2, and the activation of AP-1, NF-kB and CREB will be studied by western blotting. Signaling cascades will be studied by next generation sequencing. Expected results - Impact: The expected results will contribute to understand glucocorticoid responsiveness in COPD patients and will provide a solid basis to identify the group of COPD patients that would benefit from glucocorticoid treatment. This will greatly improve precision medicine and will significantly reduce treatment-associated side effects, costs and morbidity in COPD patients.

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