Alpha1-antitrypsin deficiency, respiratory infections and airway inflammation: the role of epithelial cells

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON35677

Source
ToetsingOnline

Brief title
AATDepithelial

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD, emphysema

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Nederlands Astma Fonds

Intervention

Keyword: alpha-1-antitrypsin, drug screening, emphysema, innate immunity

Outcome measures

Primary outcome

Bronchial biopsies will be analyzed by immunohistochemistry and digital image analysis for inflammatory cells. To allow further molecular and cellular characterization of Z-AATD-specific features of cultured bronchial epithelial cells, we will optimize a novel system to obtain bronchial epithelial cell lines with extended growth properties based on the introduction of the catalytic subunit of telomerase (hTERT) in these cells. Recent studies show that these immortalized human bronchial epithelial cells show a remarked ability for epithelial differentiation in culture, which is in contrast to other methods of immortalization previously reported.

Secondary outcome

Not applicable

Study description

Background summary

Alpha-1-Antitrypsin (AAT) is a major inhibitor of neutrophil elastase, and AAT deficiency (AATD) is associated with early-onset development of COPD. Initially it was thought that the protease-antiprotease imbalance was the main explanation for the development of emphysema in AATD. More recently, local mechanisms operative in the lung were shown to contribute to emphysema and inflammation in AATD. The most important mutation causing AATD is the Z-mutation (Z-AATD), and this is accompanied by misfolding and intracellular accumulation of the polymerized mutant AAT (Z-AAT). This process - extensively studied in hepatocytes - results in the so-called endoplasmatic reticulum (ER) stress response, causing cell death and inflammation. ER stress-induced

inflammation and cellular dysfunction may occur in the lung because lung epithelial cells and macrophages produce AAT. Indeed, studies by other researchers using cell lines from healthy subjects engineered to overexpress recombinant Z-AAT have provided preliminary evidence for altered epithelial cell function. In vivo, epithelial AAT production appears to be driven mainly by inflammatory cytokines such as oncostatin M. So far, the effect of intracellular polymerized Z-AAT on epithelial function in patients and its role in the progression of emphysema has not been studied before.

Study objective

We hypothesize that ER stress contributes to epithelial dysfunction in Z-AATD, resulting in enhanced inflammation. In addition, we hypothesize that the airways of Z-AATD patients are particularly prone to bacterial infection and colonization through the inflammatory mechanisms outlined above that result in impaired host defence. We aim to test this hypothesis by:
1. Investigating airway secretions (nasal secretions and induced sputum) from patients with Z-AATD, non-AATD COPD and healthy controls for the presence of respiratory pathogens, inflammatory mediators and effector molecules of innate immunity. Bronchial biopsies will be collected and studied in a subgroup of Z-AATD and non-Z-AATD COPD patients.
2. Exploring the ER stress response in epithelial cells from Z-AATD patients by using epithelial cell culture and investigating whether exposure to smoke or respiratory pathogens further enhances ER stress. Cellular markers of ER stress, as well as production of antimicrobial peptides will be assessed as read-out for epithelial polymerization of Z-AAT. In addition, we will explore whether a deficiency in AAT production itself (induced by siRNA) alters epithelial cell function in culture.
3. Developing a model system to study the efficacy of compounds that block AAT polymerization and increase secretion in airway epithelial cells from Z-AATD subjects. To this end we will generate epithelial cell lines from AATD patients and non-AATD COPD controls by introducing the catalytic subunit of telomerase (hTERT) in these cells

Study design

We will collect nasal secretions and induced sputum from Z-AATD and non-Z-AATD patients, as well as healthy controls. These samples will be used to compare local inflammation, antimicrobial peptides as effector molecules of innate immunity, and microbial colonization. In addition, bronchial brushes and biopsies will be collected during bronchoscopy in Z-AATD and non-Z-AATD patients to study these parameters in the bronchial mucosa (no bronchoscopy will be performed in healthy subjects for ethical reasons). In addition, bronchial epithelial cells will be isolated from the brushes to establish cell culture

Study burden and risks

There is a 20% chance patients will become desaturated during bronchoscopy, despite usual oxygen supply of 2 L/min during the bronchoscpy procedure. if this occurs, the procedure will be stopped.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-FEV1 50 to 60% of predicted value measured after inhaled bronchodilators
-A history of bronchial infections shown by at least 3 positive sputum cultures
-Stable clinical condition in the preceding 3 months

Exclusion criteria

-Asthma or any other lung disease
-Use of oral steroids in the preceding 4 weeks

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2020
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	03-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL26260.058.08