COPD: op het kruispunt van infecties en auto-immuniteit

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Universitair Ziekenhuis Gent
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Definition of COPD

Chronic obstructive pulmonary disease (COPD) is a disease state that is
– characterized by **airflow limitation**:
  - not fully reversible
  - usually progressive
– associated with an **abnormal inflammatory response** of the lungs to noxious particles or gases.

COPD is a preventable and treatable disease with some significant **extrapulmonary effects**.

**Comorbidities** and **exacerbations** contribute to the severity in individual patients.
# COPD: epidemiology

## TABLE 1

<table>
<thead>
<tr>
<th>CRD</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>300 million</td>
</tr>
<tr>
<td>COPD</td>
<td>210 million</td>
</tr>
<tr>
<td>Rhinitis (excluding asthma)</td>
<td>400 million</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>&gt;100 million</td>
</tr>
<tr>
<td>Other CRDs</td>
<td>&gt;50 million</td>
</tr>
</tbody>
</table>


INFLAMMATION

Bronchiolitis

Small airway disease
Airway inflammation
Airway remodeling

Emphysema

Parenchymal destruction
Loss of alveolar attachments
Decrease of elastic recoil

AIRFLOW LIMITATION
Diagnosis of COPD

SYMPTOMS
- cough
- sputum
- dyspnea

EXPOSURE TO RISK FACTORS
- tobacco
- occupation
- indoor/outdoor pollution

SPIROMETRY
: FEV1/FVC < 70%
Post bronchodilatation!
COPD: accelerated decline in lung function

FEV$_1$ (% of value at age 25)

Never smoked

Smoked regularly and susceptible to its effects

Stopped at 45

Stopped at 65

Disability

Death

Age (years)

Fletcher & Peto, 1977
COPD: impaired lung growth and/or accelerated decline in lung function

Local and systemic effects of COPD

- BAL / LUNG INFLAMMATION
  - INNATE
  - ADAPTIVE
- LYMPHOID FOLLICLES
- EMPHYSEMA
- AIRWAY WALL REMODELING

LOCAL (PULMONARY) EFFECTS

LOCAL (PULMONARY) EFFECTS

SYSTEMIC EFFECTS

SYSTEMIC INFLAMMATION
- BLOOD
  - Leukocytosis
- SERUM
  - TNF
  - CRP

ATHEROSCLEROSIS

MUSCLE WEAKNESS

OSTEOPOROSIS
Innate and adaptive immunity in COPD

Immunology of COPD: Overview

- Introduction
- **Innate immunity**
  - Dendritic cells
  - Adaptive immunity
  - Auto-immunity in COPD?
- Respiratory infections in COPD
- Conclusion
Chronic CS-exposure in mice is a relevant model of human COPD

<table>
<thead>
<tr>
<th></th>
<th>COPD patients</th>
<th>Smoking mice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Cigarette smoke</td>
<td>Cigarette smoke</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>chronic</td>
<td>chronic</td>
</tr>
<tr>
<td><strong>Genetic predisposition</strong></td>
<td>20% of smokers</td>
<td>strain-independent</td>
</tr>
<tr>
<td><strong>Pulmonary inflammation</strong></td>
<td>innate $\rightarrow$ adaptive immune cells</td>
<td>innate $\rightarrow$ adaptive immune cells</td>
</tr>
</tbody>
</table>
Time course of cigarette smoke-induced BAL inflammation in mice

CS-induced increase in innate inflammatory cells in BAL of wild type Balb/c and scid mice
CS-induced increase in adaptive immune cells in lungs of wild type Balb/c and scid mice

CS-induced emphysema in Balb/c and scid mice

Air

CS (Cigarette Smoke)

WT

scid

I) sensing cigarette smoke and danger signals

II) effector phase

Pro-inflammatory cytokines and chemokines (TNF-α, IL-1β, CXCL8, ...)

Proteolytic enzymes (NE, MMP-9, MMP-12, ...)

Innate immune responses in COPD
# Sensing of cigarette smoke components and Damage Associated Molecular Patterns (DAMPs) in COPD

<table>
<thead>
<tr>
<th>Cigarette smoke components</th>
<th>Receptor (cellular [soluble])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin (lipopolysaccharide)</td>
<td>TLR4 and CD14, [lipopolysaccharide-binding protein]</td>
</tr>
<tr>
<td>Nicotine</td>
<td>nAChR, TRPA1</td>
</tr>
<tr>
<td>Reactive oxygen species, free radicals</td>
<td>NLRP3</td>
</tr>
<tr>
<td>Acrolein</td>
<td>TRPA1</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbon</td>
<td>AhR</td>
</tr>
</tbody>
</table>

## DAMP released from stressed, apoptotic, and necrotic cells

<table>
<thead>
<tr>
<th>Substance</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>P2XR, P2YR</td>
</tr>
<tr>
<td>Uric acid</td>
<td>NLRP3</td>
</tr>
<tr>
<td>High-mobility group box 1</td>
<td>TLR2, TLR4, TLR9, RAGE, CD24</td>
</tr>
<tr>
<td>S100 molecules</td>
<td>TLR9, RAGE</td>
</tr>
<tr>
<td>Heat shock proteins</td>
<td>TLR2, TLR4, CD91, CD24, CD14, CD40</td>
</tr>
<tr>
<td>(\beta) defensins</td>
<td>TLR4, CCR6</td>
</tr>
<tr>
<td>Interleukin (1\alpha)</td>
<td>Interleukin 1R</td>
</tr>
<tr>
<td>DNA (mitochondrial)</td>
<td>TLR9</td>
</tr>
<tr>
<td>Formyl peptides (mitochondrial)</td>
<td>FPR1</td>
</tr>
</tbody>
</table>

## DAMP released from breakdown of ECM

<table>
<thead>
<tr>
<th>Substance</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td>TLR2, TLR4, CD44</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>TLR4, (\alpha_\beta_1) integrin, (\alpha_\beta_3) integrin</td>
</tr>
<tr>
<td>Heparan sulphate</td>
<td>TLR4</td>
</tr>
<tr>
<td>Versican</td>
<td>TLR2</td>
</tr>
<tr>
<td>Biglycan</td>
<td>TLR2, TLR4, P2XR</td>
</tr>
<tr>
<td>N-acetyl-proline-glycine-proline</td>
<td>CXCR1, CXCR2</td>
</tr>
</tbody>
</table>

Immunology of COPD: Overview

- Introduction
- Innate immunity
- **Dendritic cells**
- Adaptive immunity
- Auto-immunity in COPD?
- Respiratory infections in COPD
- Conclusion
Function of dendritic cells (DC)

Vermaelen K et al, AJRCCM 2005.
Accumulation of Dendritic Cells and Increased CCL20 Levels in the Airways of Patients with Chronic Obstructive Pulmonary Disease

Ingel K. Demedts¹, Ken R. Bracke¹, Geert Van Pottelberge¹, Dries Testelmans², Geert M. Verleden², Frank E. Vermassen³, Guy F. Joos¹, and Guy G. Brusselle¹

¹Department of Respiratory Diseases, Ghent University Hospital, Ghent; ²Department of Respiratory Diseases, Leuven University Hospital, Leuven; and ³Department of Thoracic and Vascular Surgery, Ghent University Hospital, Ghent, Belgium

Rationale: Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway inflammation. It is unclear if dendritic cells (DC) participate in this inflammatory process.

Objectives: To evaluate the presence of DC in small airways of patients with COPD.

Methods: We evaluated DC infiltration in small airways by immunohistochemistry in patients with COPD (stage I-IV), never-smokers, and smokers without COPD. Chemokine ligand 20 (CCL20, the most potent chemokine in attracting DC) was determined in total lung by RT-PCR and in induced sputum by enzyme-linked immunosorbent assay. Chemokine receptor 6 (CCR6, the receptor for CCL20) expression on human pulmonary DC was evaluated by RT-PCR and flow cytometry.

Measurements and Main Results: There is a significant increase in DC number in the epithelium (p = 0.007) and adventitia (p = 0.009) of small airways of patients with COPD compared with never-smokers and smokers without COPD. DC number in epithelium and adventitia increases along with disease severity. CCL20 mRNA expression in total lung and CCL20 protein levels in induced sputum are significantly higher in patients with COPD compared with never-smokers.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway inflammation. Macrophages, neutrophils, and CD8⁺ T cells participate in this inflammatory process. It is unclear if dendritic cells (DC) are involved in the chronic airway inflammation in COPD.

What This Study Adds to the Field

There is accumulation of DC in COPD airways, which increases with disease severity. It is demonstrated that CCL20 (the most important chemokine for attracting DC) is elevated in COPD lungs and DC express CCR6 (receptor for CCL20).
Time course of the effect of cigarette smoke exposure on dendritic cell number in BAL

Accumulation of Langerin+ dendritic cells in small airways of COPD patients

Never smoker

“Healthy” Smoker

COPD GOLD I

COPD GOLD II

COPD GOLD III

COPD GOLD IV

Dendritic cells in BAL fluid of CS-exposed mice show increased expression of MHC class II and costimulatory molecules.

Pulmonary dendritic cells express MMP-12 mRNA

Dendritic cells drive CD4+ T helper cell differentiation

Immunology of COPD: Overview

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Innate immunity

Dendritic cells

Adaptive immunity

Auto-immunity in COPD?

Respiratory infections in COPD

Conclusion
Adaptive immune responses in COPD

Lymphoid follicles in patients with severe COPD

Lymphoid (B-cell) follicles in murine lung tissue after 2-6 months smoke exposure

The development of B-cell follicles is progressive with time and correlates with the increase in airspace enlargement.

Correlation ↔ causal association?

Van der Strate B. et al, AJRCCM 2006; 751-758.
CS-induced increase in lymphoid follicles

Lm: wild type:
Air: 38.1 µm
CS: 41.6 µm
p<0.01

Lm: scid:
Air: 38.3 µm
CS: 41.4 µm
p<0.05

REVIEW

Lymphoid follicles in (very) severe COPD: beneficial or harmful?


ABSTRACT: Inflammation is a main pathogenetic factor in the development and progression of chronic obstructive pulmonary disease (COPD). Recently, it has become clear that not only the innate, but also the specific immune response plays a role. A striking finding, in particular in lungs of patients with severe COPD, often with a predominant emphysema phenotype, is the presence of B-cell follicles. As seen in other tissues, these follicles are the result of lymphoid neogenesis. The finding of oligoclonality in B-cell follicles in COPD suggests that they play a role in local antigen specific immune responses. To date, it is not known which antigens may be involved; microbial antigens, cigarette smoke-derived antigens and antigens from extracellular matrix breakdown products have been suggested. Consequently, the pathogenetic role of this follicular B-cell response is not yet clear. It might be protective against microbial colonisation and infection of the lower respiratory tract and, therefore, beneficial, or it could be of a more harmful (autoimmune) nature, directed against lung tissue components. It is necessary to determine the specific antigen(s) and to explore the exact role of the COPD related B-cell response in order to include modulation of this response and develop therapeutic options.
Drivers of adaptive immune responses in COPD?

- Cigarette smoke components (eg tobacco glycoprotein)?
+ Bacterial colonization (eg H. influenzae)
+ Viral infections (eg adenovirus)
- Breakdown products of extracellular matrix (eg elastin fragments)
- Autoimmunity? Self (neo)antigens?
Immunology of COPD: Overview

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Autoimmune disease: definition

- A chronic inflammatory process leading to progressive tissue damage
- *Induced* by an interaction of a *genetic predisposition* and *exogenic factors*
- *Persistent* even when the initial inciting agent has disappeared (e.g., smoking cessation)
- *Mediated* by *adaptive immune mechanisms* (auto-antibodies, autoreactive T cells)

→ Sequence of events!
Pathogenesis of rheumatoid arthritis

Autoantibodies before SLE

Antielastin autoimmunity in tobacco smoking–induced emphysema

Seung-Hyo Lee¹, Sangeeta Goswami², Ariel Grudo¹, Li-zhen Song¹, Venkata Bandi¹, Sheila Goodnight-White¹, Linda Green³, Joan Hacken-Bitar⁴, Joseph Huh⁵,⁶, Faisal Bakaeen⁵,⁶, Harvey O Coxson⁷, Sebastian Cogswell⁷, Claudine Storness-Bliss⁷, David B Corry¹,² & Farrah Kheradmand¹,²

Chronic obstructive pulmonary disease and emphysema are common destructive inflammatory diseases that are leading causes of death worldwide. Here we show that emphysema is an autoimmune disease characterized by the presence of antielastin antibody and T-helper type 1 (TH1) responses, which correlate with emphysema severity. These findings link emphysema to adaptive immunity against a specific lung antigen and suggest the potential for autoimmune pathology of other elastin-rich tissues such as the arteries and skin of smokers. Nat Med 2007; 13: 567-69.
Innate and adaptive immune responses in COPD

Anti-Proline-Glycine-Proline or Antielastin Autoantibodies Are Not Evident in Chronic Inflammatory Lung Disease

Catherine M. Greene*, Teck Boon Low*, Shane J. O’Neill, and Noel G. McElvaney

1Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland

Rationale: In patients with chronic inflammatory lung disease, pulmonary proteases can generate neoantigens from elastin and collagen with the potential to fuel autoreactive immune responses. Antielastin peptide antibodies have been implicated in the pathogenesis of tobacco-smoke–induced emphysema. Collagen-derived peptides may also play a role.

Objectives: To determine whether autoantibodies directed against elastin- and collagen-derived peptides are present in plasma from three groups of patients with chronic inflammatory lung disease compared with a nonsmoking healthy control group and to identify whether autoimmune responses to these peptides may be an important component of the disease process in these patients.

Methods: A total of 124 patients or healthy control subjects were recruited for the study (Z-A1AT deficiency, n = 20; cystic fibrosis, n = 40; chronic obstructive pulmonary disease, n = 31; healthy control, 33).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject
Autoimmune responses to elastin- and collagen peptides may have a role in the pathogenesis of tobacco-smoke-induced emphysema.

What This Study Adds to the Field
We demonstrate no evidence for systemic autoantibodies directed against elastin peptides or N-acetylated-proline-glycine-proline in chronic inflammatory lung disease.
ORIGINAL ARTICLE

Antielastin B-cell and T-cell immunity in patients with chronic obstructive pulmonary disease

Manuela Rinaldi,1 An Lehouck,1 Nele Heulens,1 Renaud Lavend’Homme,2 Vincent Carlier,2 Jean-Marie Saint-Remy,2 Marc Decramer,1 Ghislaine Gayan-Ramirez,1 Wim Janssens

ABSTRACT

Rationale Antielastin autoimmunity has been hypothesised to drive disease progression in chronic obstructive pulmonary disease (COPD). The proposed mechanism is currently disputed by conflicting data. The authors aimed to explore antibody responses against elastin in a large and extensively characterised COPD population and to assess elastin-specific peripheral T-cell reactivity in a representative subgroup.

Methods Antielastin antibodies were analysed by indirect ELISA on the plasma of 320 patients with COPD (Global Initiative for Chronic Obstructive Lung Disease 1—4) and 143 smoking controls. In a second group of 40 patients with COPD and smoking controls, T-cell responses against extracellular matrix (elastin, collagen I and collagen V) were determined with enzyme-linked immunosorbent spot (ELISpot) (interferon γ (IFN-γ) and interleukin-2) on peripheral blood mononuclear cells and compared with the responses of 11 never-smoking controls.

Results Antielastin antibody titres were not elevated in patients with COPD compared with smoking controls and even decreased significantly with increasing severity of

Key messages

What is the key question?

- Is chronic obstructive pulmonary disease (COPD) characterised by a peripheral immune response against elastin?

What is the bottom line?

- Lung destruction in COPD may lead to the release of self-antigens.
- This study investigated whether elastin and other components of the extracellular matrix are inducing a T-cell and B-cell immune response, which may be specific for COPD.

Why read on?

- Our study shows that a systemic immune response against elastin fragments was not present in patients with COPD.
- However, smoke-induced T-cell immunity against collagen V was found to be more prevalent in smokers and needs further attention.
Anti-Tissue Antibodies Are Related to Lung Function in Chronic Obstructive Pulmonary Disease

Belén Núñez1,2,3, Jaume Sauleda1,2,3, Josep Maria Antó4,5,6,7, Maria Rosa Julià8, Mauricio Orozco3,4,9, Eduard Monsó3,10, Aina Noguera2,3,11, Federico P. Gómez3,12, Judith Garcia-Aymerich4,5,6,7, and Alvar Agustí2,3,12,13, on behalf of the PAC-COPD Investigators*

1Servei Pneumologia, 8Servei Immunologia, and 11Servei Anàlisi Clínicas, Hospital Universitari Son Dureta, Palma de Mallorca, Spain; 2Fundació Cautet-Cimera, Bunyola, Spain; 3CIBER Enfermedades Respiratorias; 4Centre for Research in Environmental Epidemiology; 5Municipal Institute of Medical Research (IMIM-Hospital del Mar); 6Department of Experimental and Health Sciences, Universitat Pompeu Fabra; 7CIBER Epidemiologia y Salud Pública, Barcelona, Spain; 9Servei Pneumologia, Hospital del Mar, Barcelona, Spain; 10Hospital Germans Trias i Pujol, Badalona; 12Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; 13Thorax Institute, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Rationale: Chronic obstructive pulmonary disease (COPD) is a multi-component disease. Autoimmunity can contribute to the pathogenesis of COPD.

Objectives: This study investigates the prevalence of circulating antinuclear antibodies (ANA) and anti-tissue (AT) antibodies, two common markers of autoimmunity, in COPD and their relationship with several components of the disease.

Methods: We determined lung function, the serum titers of ANA and AT by immunofluorescence, and the serum levels of C-reactive protein (CRP) by high sensitivity nephelometry in 328 patients with clinically stable COPD and in 67 healthy controls recruited in the PAC-COPD study. Multiple linear and logistic regression analysis was used to analyze results.

Measurements and Main Results: The prevalence of abnormal ANA and AT titers was 34% and 26% in patients and 3% and 6% in controls, respectively. Levels of AT greater than or equal to 1:320 were seen in 21% of patients with COPD and were independently associated with the severity of airflow limitation and gas transfer impairment (P < 0.05). Neither ANA or AT titers was related to body mass index, current smoking status, use of inhaled steroids, the Charlson index, or serum C-reactive protein values.

AT A GLANCE CLINICAL COMMENTARY

Scientific Knowledge on the Subject
Autoimmunity can contribute to the pathogenesis of chronic obstructive pulmonary disease (COPD). The prevalence of circulating antinuclear and anti-tissue antibodies in COPD, and their potential relationship with other domains of the disease, is unknown.

What This Study Adds to the Field
Our results show that between a third and a quarter of patients with clinically stable COPD present abnormal levels of circulating antinuclear and anti-tissue antibodies, the latter being related to lung function impairment. These observations provide further support to the hypothesis that the pathogenesis of COPD involves an autoimmune component.
AntiNuclear Antibodies (ANA) in COPD

AntiTissue Antibodies (AT) in COPD

The paradigm of autoimmune disease

Gene → autoantibody → Disease

environment → autoantibody → Disease
The paradigm of autoimmune disease

Gene

environment

Specific autoantibody

Disease

Non-specific autoantibody
What constitutes a specific autoantibody?

<table>
<thead>
<tr>
<th>Non-Specific</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-reactive</td>
<td>Antigen-specific</td>
</tr>
<tr>
<td>Present in other autoimmune diseases</td>
<td>Disease or subset specific</td>
</tr>
<tr>
<td>Low titre (2-3 x normal)</td>
<td>High titre (&gt;10x normal)</td>
</tr>
<tr>
<td>Of little clinical use</td>
<td>Used in clinical diagnosis</td>
</tr>
<tr>
<td>Results from tissue injury or polyclonal activation</td>
<td>Likely to be involved in pathogenesis.</td>
</tr>
<tr>
<td>Heterogeneous antigens</td>
<td>Family of biologically related proteins</td>
</tr>
</tbody>
</table>
Immunology of COPD: Overview

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- Adaptive immunity
- Auto-immunity in COPD?
- Respiratory infections in COPD
- Conclusion
Disordered Microbial Communities in Asthmatic Airways

Markus Hilty¹, Conor Burke², Helder Pedro³, Paul Cardenas¹, Andy Bush¹, Cara Bossley¹, Jane Davies¹, Aaron Ervine², Len Poulter², Lior Pachter⁴, Miriam F. Moffatt¹, William O. C. Cookson¹*

¹ National Heart and Lung Institute, Imperial College London, London, England, ² Department of Respiratory Medicine, Connolly Hospital, Dublin, Ireland, ³ Instituto Gulbenkian de Ciência, Instituto de Tecnologia Química e Biológica, Oeiras, Portugal, ⁴ Department of Mathematics, University of California, Berkeley, California, United States of America

Abstract

**Background:** A rich microbial environment in infancy protects against asthma [1,2] and infections precipitate asthma exacerbations [3]. We compared the airway microbiota at three levels in adult patients with asthma, the related condition of COPD, and controls. We also studied bronchial lavage from asthmatic children and controls.

**Principal Findings:** We identified 5,054 16S rRNA bacterial sequences from 43 subjects, detecting >70% of species present. The bronchial tree was not sterile, and contained a mean of 2,000 bacterial genomes per cm² surface sampled. Pathogenic Proteobacteria, particularly *Haemophilus* spp., were much more frequent in bronchi of adult asthmatics or patients with COPD than controls. We found similar highly significant increases in Proteobacteria in asthmatic children. Conversely, Bacteroidetes, particularly *Prevotella* spp., were more frequent in controls than adult or child asthmatics or COPD patients.

**Significance:** The results show the bronchial tree to contain a characteristic microbiota, and suggest that this microbiota is disturbed in asthmatic airways.

M. Hilty et al, Plos One 2010; 5: e8578.
Distribution of common bacterial phyla and genera in normal and diseased bronchi

M. Hilty et al, Plos One 2010; 5: e8578.
# Pathogen Associated Molecular Patterns (PAMPs) and Pattern Recognition Receptors (PRR) in COPD

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>PAMPs</th>
<th>PRR (cellular [soluble])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Lipoteichoic acid, pneumolysin, Peptidoglycan, CpG dinucleotides, Phosphorylcholine</td>
<td>TLR2, TLR4, PAFR, NOD1, NOD2, [LBP]</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>LPS, OMP P6, OMP P2, Peptidoglycan</td>
<td>TLR4 and CD14, [LBP], TLR2, NOD1, NOD2</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>LPS, Usp A1, Usp A2</td>
<td>TLR4 and CD14, [LBP], NOD1, NOD2, CAECAM1, PAFR</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>LPS, Flagellin</td>
<td>TLR4 and CD14, [LBP], TLR5</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>dsRNA</td>
<td>TLR3, MDA5</td>
</tr>
<tr>
<td>Influenza</td>
<td>dsRNA, ssRNA</td>
<td>TLR3, RIG-I, MDA5, TLR7, TLR8</td>
</tr>
</tbody>
</table>
Defective macrophage phagocytosis of bacteria in COPD

Macrolides stimulate phagocytosis of bacteria by macrophages

Mucosal IgA switching and secretory IgA (slgA) epithelial transcytosis via plgR

Cerutti A. Nat Rev Immunol 2008; 8: 421-34.
Bronchial secretory IgA deficiency in COPD

Deficiency of secretory IgA (SIgA) in BAL fluid of COPD

Vicious-circle hypothesis of infection and inflammation in COPD

Initiating factors
(e.g., smoking, childhood respiratory disease)

Impaired innate lung defense

Microbial colonization

Microbial antigens

PAMPs

DAMPs
Altered proteinase-antiproteinase antibody balance

Increased proteolytic activity

Acute exacerbation

Inflammatory response

Airway epithelial injury

Progression of COPD

S. Sethi and T. Murphy, NEJM 2008; 359: 2355-65.
Azithromycine ter preventie van exacerbaties bij COPD

Experimental rhinovirus infection in subjects with COPD causes exacerbations

Experimental rhinovirus infection in subjects with COPD causes exacerbations

Immunology of COPD: Overview

- Introduction
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- Dendritic cells
- Adaptive immunity
- Auto-immunity in COPD?
- Respiratory infections in COPD

Conclusion
Cigarette smoke activates innate immune cells (macrophages, neutrophils and epithelial cells) by triggering Pathogen Recognition Receptors:

– directly (e.g. LPS, oxidative stress) or
– indirectly (via DAMPs).

Defective macrophage phagocytosis of bacteria and apoptotic cells in COPD.
Immunology of COPD: conclusions (2)

- **Dendritic cells** accumulate in the lungs of CS-exposed mice and in the small airways of patients with (severe) COPD.

- Chronic **adaptive immune** responses (Th1 and Th17 CD4+ cells, cytotoxic CD8+ cells and B cells) lead to the development of lymphoid follicles.
Autoantibodies are present in a subgroup of patients with severe COPD (emphysema): pathogenic?

The sequence of events in the pathogenesis of RA (rheumatoid arthritis) and COPD is different:

- RA: auto-antibodies $\rightarrow$ articular inflammation and destruction
- COPD: pulmonary inflammation and destruction $\rightarrow$ auto-antibodies?
Viral and bacterial infections of the respiratory tract:
- cause acute exacerbations of COPD (proof of concept: Rhinovirus)
- amplify and perpetuate chronic inflammation in stable COPD (via PAMPs).

Deficiency of bronchial secretory IgA in COPD.
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Ghent University, Ghent, Belgium

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Dr J Heeringa           Mevr J verkroost

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Immunopathology of COPD

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<tr>
<th></th>
<th>Innate immunity</th>
<th>Adaptive immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognition</td>
<td></td>
<td><strong>Adaptive immunity</strong></td>
</tr>
<tr>
<td>Receptors</td>
<td>Pattern recognition receptors</td>
<td>T-cell and B-cell receptors</td>
</tr>
<tr>
<td>Molecules</td>
<td>Pathogen-associated molecular patterns; damage-associated molecular patterns</td>
<td>Processed antigens; antigen-antibody complexes</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td><strong>Adaptive immunity</strong></td>
</tr>
<tr>
<td>Onset</td>
<td>Immediate</td>
<td>Delayed (4–5 days)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Fixed repertoire</td>
<td>Specific</td>
</tr>
<tr>
<td>Immunological memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ontology</td>
<td>Ancient</td>
<td>Recent</td>
</tr>
<tr>
<td><strong>Cellular component</strong></td>
<td></td>
<td><strong>Adaptive immunity</strong></td>
</tr>
<tr>
<td>Haematopoietic</td>
<td>Neutrophils, macrophages, dendritic cells, eosinophils, natural killer cells</td>
<td>T lymphocytes, B lymphocytes</td>
</tr>
<tr>
<td>Structural</td>
<td>Epithelial cells</td>
<td>Follicular dendritic cells</td>
</tr>
<tr>
<td>Effector molecules</td>
<td>Acute phase proteins, complement, cytokines, chemokines, growth factors, antimicrobial peptides</td>
<td>B cells: immunoglobulins (antibodies) CD4+ T cells: Th1, Th2, Th17, Treg cytokines CD8+ T cells: perforins, granzymes (cytotoxicity)</td>
</tr>
</tbody>
</table>