Translational research in asthma and COPD

Guy Brusselle, MD, PhD
Department of Respiratory Medicine
Ghent University

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I) Translational research in COPD: overview

- Introduction
- Genetic susceptibility
- Epigenetics
- Pulmonary inflammation: Lymphoid follicles
- Systemic inflammation: Comorbidities
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.
INFLAMMATION

Bronchiolitis

Small airway disease
Airway inflammation
Airway remodeling

Parenchymal destruction
Loss of alveolar attachments
Decrease of elastic recoil

Emphysema

AIRFLOW LIMITATION
COPD: accelerated decline in lung function

FEV₁ (% 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
I) Translational research in COPD: overview

- Introduction

**Genetic susceptibility:**
- Candidate gene approach
- Genome Wide Association (GWA) studies

- Epigenetics

- Pulmonary inflammation: Lymphoid follicles

- Systemic inflammation: Comorbidities
I) Why do only 20% of smokers develop COPD?
Laboratory for Translational research of Obstructive Pulmonary diseases
Department of Respiratory Medicine, Ghent University Hospital

Candidate gene approach:
1) Matrix MetalloProteinase 12 (MMP12)
2) C-reactive protein (CRP)
Requirement for Macrophage Elastase for Cigarette Smoke–Induced Emphysema in Mice

R. Dean Hautamaki, Dale K. Kobayashi, Robert M. Senior, Steven D. Shapiro*

To determine which proteinases are responsible for the lung destruction characteristic of pulmonary emphysema, macrophage elastase–deficient (MME\(^{-/-}\)) mice were subjected to cigarette smoke. In contrast to wild-type mice, MME\(^{-/-}\) mice did not have increased numbers of macrophages in their lungs and did not develop emphysema in response to long-term exposure to cigarette smoke. Smoke-exposed MME\(^{-/-}\) mice that received monthly intratracheal instillations of monocyte chemoattractant protein–1 showed accumulation of alveolar macrophages but did not develop air space enlargement. Thus, macrophage elastase is probably sufficient for the development of emphysema that results from chronic inhalation of cigarette smoke.

MMP-12 protein levels in induced sputum

MMP12, Lung Function, and COPD in High-Risk Populations

Gary M. Hunninghake, M.D., M.P.H., Michael H. Cho, M.D., M.P.H., Yohannes Tesfaigzi, Ph.D., Manuel E. Soto-Quiros, M.D., Ph.D., Lydiana Avila, M.D., Jessica Lasky-Su, Sc.D., Chris Stidley, Ph.D., Erik Melén, M.D., Ph.D., Gilla Söderhäll, Ph.D., Jenny Hallberg, Ph.D., Inger Kull, R.N., Ph.D., Juha Kere, M.D., Ph.D., Magnus Svartengren, M.D., Ph.D., Göran Pershagen, M.D., Ph.D., Magnus Wickman, M.D., Ph.D., Christoph Lange, Ph.D., Dawn L. Demeco, M.D., M.P.H., Craig P. Hersh, M.D., M.P.H., Barbara J. Klanderman, Ph.D., Benjamin A. Raby, M.D., M.P.H., David Sparrow, D.Sc., Steven D. Shapiro, M.D., Edwin K. Silverman, M.D., Ph.D., Augusto A. Litonjua, M.D., M.P.H., Scott T. Weiss, M.D., and Juan C. Celedón, M.D., Dr.P.H.
Effect of genetic factors and smoking on lung function

Huge need of translational research due to Genome-Wide Association (GWA) studies
CHARGE consortium: Cohorts for Heart and Aging Research in Genomic Epidemiology

- Rotterdam Study (RS I and II)
- Framingham Heart Study (FHS)
- Cardiovascular Health Study (CHS)
- Atherosclerosis Risk in Communities (ARIC) Study
Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function

Dana B Hancock¹,²,²⁹*, Mark Eijgelsheim²,³,³⁹, Jemma B Wilk³,²⁹, Sina A Gharib⁴,⁵,³⁹, Laura R Loehr¹,⁶, Kristin D Marciano³⁷,³⁷, Nora Franceschini⁶, Yannick M T A van Durme²,⁸, Ting-hsu Chen⁹,¹⁰, R Graham Barr¹¹–¹⁵, Matthew B Schabath¹⁴, David J Couper¹⁵, Guy G Brusselle²,⁸, Bruce M Psaty⁵,⁷,¹⁶–¹⁸, Cornelia M van Duijn², Jerome I Rotter¹⁹, André G Uitterlinden²,²⁰, Albert Hofman², Naresh M Punjabi²¹, Fernando Rivadeneira²,²², Alanna C Morrison²², Paul L Enright²³, Kari E North⁶,²⁴, Susan R Heckbert⁷,¹⁶,¹⁷, Thomas Lumley²⁵,³⁰, Bruno H C Stricker²,²⁰,²⁶,²⁷,³⁰, George T O’Connor⁹,¹⁰,³⁰ & Stephanie J London¹,²⁸,³⁰

Spirometric measures of lung function are heritable traits that reflect respiratory health and predict morbidity and mortality. We meta-analyzed genome-wide association studies for two clinically important lung function measures: forced expiratory volume in the first second (FEV₁) and its ratio to forced vital capacity (FEV₁/FVC), an indicator of airflow obstruction. This meta-analysis included 20,890 participants of European ancestry from four CHARGE Consortium studies: Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study and Rotterdam Study. We identified eight loci associated with FEV₁/FVC (HHIP, GPR126, ADAM19, AGER-PPT2, FAM13A, PITCH1, PID1 and HTR4) and one locus associated with FEV₁ (INTS12-GSTCD-NPP7) at or near genome-wide significance ($P < 5 \times 10^{-8}$) in the CHARGE Consortium dataset. Our findings may offer insights into pulmonary function and pathogenesis of chronic lung disease.
Association of 8 genes with FEV$_1$/FVC

Physiologic Hedgehog Signaling (Ligand-Dependent)

Lung development: branching and septation

Hedgehog interacting protein (HHIP) gene and COPD

Rotterdam Study

Bergen Case Control Population

NETT/NAS

Overall 0.77 (0.70 - 0.84)

Y. Van Durme et al, ERJ 2010; 36: 89-95.
Genome-wide association (GWA) study of FEV₁/FVC

Lung development: branching morphogenesis

Maternal Vitamin A Supplementation and Lung Function in Offspring

William Checkley, M.D., Ph.D., Keith P. West, Jr., Dr.P.H., Robert A. Wise, M.D., Matthew R. Baldwin, M.D., Lee Wu, M.H.S., Steven C. LeClerq, M.I.I.S., Parul Christian, Dr.P.H., Joanne Katz, Sc.D., James M. Tielsch, Ph.D., Subarna Khatry, M.D., and Alfred Sommer, M.D., M.H.S.

ABSTRACT

BACKGROUND
Vitamin A is important in regulating early lung development and alveolar formation. Maternal vitamin A status may be an important determinant of embryonic alveolar formation, and vitamin A deficiency in a mother during pregnancy could have lasting adverse effects on the lung health of her offspring. We tested this hypothesis by examining the long-term effects of supplementation with vitamin A or beta-carotene in women before, during, and after pregnancy on the lung function of their offspring, in a population with chronic vitamin A deficiency.

METHODS
We examined a cohort of rural Nepali children 9 to 13 years of age whose mothers had participated in a placebo-controlled, double-blind, cluster-randomized trial of vitamin A or beta-carotene supplementation between 1994 and 1997.
Maternal vitamin A supplementation and lung function in offspring

Curves of lung function growth

Weiss S., AJRCCM 2010; 181: 1170-73.
COPD: decline in lung function

FEV\textsubscript{1} (% of value at age 25)

Effect of genetic factors and environmental exposures on lung function

Distribution of annual change in \( \text{FEV}_1 \) in patients with COPD

II) Why does COPD persist despite smoking cessation?
Adaptive immune responses in COPD

I) Translational research in COPD: overview

- Introduction
- Genetic susceptibility
- **Epigenetics**
- Pulmonary inflammation: Lymphoid follicles
- Systemic inflammation: Comorbidities
MicroRNA

- Small non-coding RNAs:
  - 19-25 nucleotides & single stranded

- Bind to the 3’ UTR of messenger RNA in a complementary way

- Induce degradation of messenger RNA and/or

- Block translation process

- **Pleiotropy**: one microRNA can
  - regulate several gene products and
  - interfere with several biological processes.
Can we detect microRNA in induced sputum?

- # miRNA tested: 624
- # miRNA detected: 212 = 33%
- Normalization:
  - Control small RNA:
    6 tested, 3 detected
  - Mean expression level of all microRNAs per sample (geNorm analysis)

### miRNA expression in COPD vs Never Smoker

<table>
<thead>
<tr>
<th>Unique ID</th>
<th>p value M-W-U</th>
<th>CS eff</th>
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<tbody>
<tr>
<td>hsa-miR-34c</td>
<td>↓ 0.0003</td>
<td>#</td>
</tr>
<tr>
<td>hsa-miR-218</td>
<td>↓ 0.00043</td>
<td>#</td>
</tr>
<tr>
<td>hsa-miR-34b</td>
<td>↓ 0.00043</td>
<td>#</td>
</tr>
<tr>
<td>hsa-let-7c</td>
<td>↓ 0.0006</td>
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<tr>
<td>hsa-miR-342-3p</td>
<td>↓ 0.0006</td>
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<tr>
<td>hsa-miR-125a-5p</td>
<td>↓ 0.000832</td>
<td></td>
</tr>
<tr>
<td>hsa-miR30e-3p</td>
<td>↓ 0.001129</td>
<td>#</td>
</tr>
<tr>
<td>hsa-miR-125b</td>
<td>↓ 0.001519</td>
<td>#</td>
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</table>
Correlation between micro-RNA and FEV$_1$

Hsa-Let-7c: targets

- HMGA2: high mobility group A2
- LIN28b: overexpression in primary human tumors
- Insulin like growth factor-2 mrna binding protein: regulating translation of IGF
- TNFalpha receptor-II
- TGFbeta receptor-1
- ADAMTS8
- HAS-2
- ARID-3b: embryogenesis, transcription regulation, chromatin structure modification
Let-7c expression: in situ hybridisation

Let-7c regulates sTNFR-II

Conclusions: miRNA in COPD

- **MicroRNAs** are present in induced sputum supernatant.

- Downregulation of many miRNAs in **current smokers**: impaired control of translation in biological processes such as cell growth and inflammation → smoking induced lung diseases (cancer, COPD).

- **COPD**: 6 miRNAs are independently associated with FEV₁ (% predicted).
Conclusions: miRNA in COPD

- Reduction of let-7c and miR-125b in smokers with COPD is confirmed in a validation cohort.
- Targets of let-7c are enriched in sputum transcriptome of patients with COPD.
- Let-7c expression is inversely associated with sTNFR-II in induced sputum.
- Let-7c expression is confirmed by *in situ* hybridisation in sputum bronchial epithelial cells and macrophages.
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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.

Role of CXCL13 in Cigarette Smoke–induced Lymphoid Follicle Formation and Chronic Obstructive Pulmonary Disease

Ken R. Bracke\textsuperscript{1*}, Fien M. Verhamme\textsuperscript{1*}, Leen J. M. Seys\textsuperscript{1}, Claudie Bantsimba-Malanda\textsuperscript{2}, Danen Mootooosamy Cunoosamy\textsuperscript{3}, Ronald Herbst\textsuperscript{2}, Hamida Hammad\textsuperscript{4,5}, Bart N. Lambrecht\textsuperscript{4,5}, Guy F. Joos\textsuperscript{1}, and Guy G. Brusselle\textsuperscript{1}

\textsuperscript{1}Laboratory for Translational Research in Obstructive Pulmonary Diseases, Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; \textsuperscript{2}Department of Research, MedImmune, LLC, Gaithersburg, Maryland; \textsuperscript{3}AstraZeneca R&I iMed, Molndal, Sweden; \textsuperscript{4}Laboratory of Immunoregulation and Mucosal Immunity, Department for Molecular Biomedical Research, VIB, Ghent, Belgium; and \textsuperscript{5}Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

\textit{Rationale:} The B cell–attracting chemokine CXCL13 is an important mediator in the formation of tertiary lymphoid organs (TLOs). Increased numbers of ectopic lymphoid follicles have been observed in lungs of patients with severe chronic obstructive pulmonary disease (COPD). However, the role of these TLOs in the pathogenesis of COPD remains unknown.

\textit{Objectives:} By neutralizing CXCL13 in a mouse model of chronic cigarette smoke (CS) exposure, we aimed at interrogating the link between lymphoid follicles and development of pulmonary inflammation, emphysema, and airway wall remodeling.

\textit{Methods:} We first quantified and localized CXCL13 in lungs of air- or CS-exposed mice and in lungs of never smokers, smokers without airflow obstruction, and patients with COPD by reverse transcriptase–polymerase chain reaction, ELISA, and immunohistochemistry. Next, CXCL13 signaling was blocked by prophylactic or therapeutic administration of anti-CXCL13 antibodies in mice exposed to air or CS for 24 weeks, and several hallmarks of COPD were evaluated.

\textit{Measurements and Main Results:} Both mRNA and protein levels of CXCL13 were increased in lungs of CS-exposed mice and patients with COPD. Importantly, expression of CXCL13 was observed within B-cell areas of lymphoid follicles. Prophylactic and therapeutic ad-
Increased expression of CXCL13 in COPD

Increased expression of CXCL13 in murine model of COPD

Neutralization of CXCL13 prevents lymphoid follicle formation in murine model of COPD

Effect of anti-CXCL13 on BAL inflammation

Effect of anti-CXCL13 on emphysema

Neutralization of CXCL13 decreases IgA levels in BAL of CS-exposed mice

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Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype


1 Thorax Institute, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona and Centro de Investigación en red de enfermedades respiratorias (CIBERES), Barcelona, Spain; 2 Fundación Investigación Sanitaria Illes Balears (FISIB), Palma de Mallorca, Spain; 3 GlaxoSmithKline, Research Triangle Park, North Carolina, United States of America; 4 University of Nebraska Medical Center, Omaha, Nebraska, United States of America; 5 University of Edinburgh, Edinburgh, UK; 6 GlaxoSmithKline, King of Prussia, Pennsylvania, United States of America; 7 Respiratory Section, Hvidovre Hospital/University of Copenhagen, Denmark; 8 Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK; 9 University of Cambridge, Cambridge, UK; 10 University of Liverpool, Liverpool, UK; 11 University of Maastricht, Maastricht, The Netherlands; 12 Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, United States of America; 13 University of British Columbia, Vancouver, Canada; 14 University of Bergen, Bergen, Norway

Abstract

Background: Because chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, the identification of specific clinical phenotypes is key to developing more effective therapies. To explore if the persistence of systemic inflammation is associated with poor clinical outcomes in COPD we assessed patients recruited to the well-characterized ECLIPSE cohort (NCT00292552).

Methods and Findings: Six inflammatory biomarkers in peripheral blood (white blood cells (WBC) count and CRP, IL-6, IL-8, fibrinogen and TNF-α levels) were quantified in 1,755 COPD patients, 297 smokers with normal spirometry and 202 non-smoker controls that were followed-up for three years. We found that, at baseline, 30% of COPD patients did not show evidence of systemic inflammation whereas 16% had persistent systemic inflammation. Even though pulmonary abnormalities were similar in these two groups, persistently inflamed patients during follow-up had significantly increased all-cause mortality (13% vs. 2%, p<0.001) and exacerbation frequency (1.5 (1.5) vs. 0.9 (1.1) per year, p<0.001) compared to non-inflamed ones. As a descriptive study our results show associations but do not prove causality. Besides this, the inflammatory response is complex, and we studied only a limited panel of biomarkers, albeit they are those investigated by the majority of previous studies and are often and easily measured in clinical practice.

Conclusions: Overall, these results identify a novel systemic inflammatory COPD phenotype that may be the target of specific research and treatment.
Serum biomarkers in COPD patients, smokers and nonsmokers

Network of systemic inflammatory response in COPD patients and controls

Prevalence, Incidence, and Lifetime Risk for the Development of COPD in the Elderly

The Rotterdam Study

Yannick M. T. A. van Durme, MD; Katia M. C. Verhamme, MD, PhD; Theo Stijnen, MD, PhD; Frank J. A. van Rooij, DSc; Geert R. Van Pottelberge, MD; Albert Hofman, MD, PhD; Guy F. Joos, MD, PhD, FCCP; Bruno H. Ch. Stricker, MB, PhD; and Guy G. Brusselle, MD, PhD

Background: COPD is a major cause of chronic morbidity and mortality throughout the world. Although the prevalence of COPD is already well documented, there are only few studies regarding the incidence of COPD.

Methods: In a prospective population-based cohort study among subjects aged ≥ 55 years, COPD was diagnosed with an algorithm based on the validation of hospital discharge letters, files from the general practitioner, and spirometry reports.

Results: In this study cohort of 7,983 participants, 648 cases were identified with incident COPD after a median follow-up time of 11 years (interquartile range, 7.8 years). This resulted in an overall incidence rate (IR) of 9.2/1,000 person-years (PY) [95% confidence interval (CI), 8.5 to 10.0]. The IR of COPD was higher among men (14.4/1,000 PY; 95% CI, 13.0 to 16.0) than among women (6.2/1,000 PY; 95% CI, 5.5 to 7.0), and higher in smokers than in never-smokers (12.8/1,000 PY; 95% CI, 11.7 to 13.9 and 3.8/1,000 PY; 95% CI, 3.2 to 4.7, respectively). Remarkable was the high incidence in the youngest female age category of 55 to 59 years (7.4/1,000 PY; 95% CI, 4.1 to 12.6). For a 55-year-old man and woman still free of COPD at cohort entry, the risk for the development of COPD over the coming 40 years was 24% and 16%, respectively.

Conclusion: The overall incidence of COPD in an elderly population is 9.2/1,000 PY, with a remarkably high incidence in the youngest women, suggesting a further shift toward the female sex in the gender distribution of COPD. During their further lives, one of four men and one of six women free of COPD at the age of 55 years will have COPD develop.

(CHEST 2009; 135:368–377)
COPD and Co-Morbidities

COPD patients are at increased risk for:

- Cardiovascular diseases: myocardial infarction, angina
- Metabolic syndrome, Diabetes
- Depression
- Osteoporosis
- Skeletal muscle dysfunction
- Respiratory infections
- Lung cancer
- **Stroke**
COPD and Carotid artery plaques: OBJECTIVES

1) COPD and the prevalence of Carotid wall thickening

2) COPD and the composition of Carotid artery plaques
   - Calcification
   - Intraplaque hemorrhage
   - Lipid Core

3) The influence of frequent exacerbations on both associations

COPD and Carotid artery plaques: Study profile

1386 subjects with interpretable spirometry

213 subjects excluded (asthma, suggestive of restrictive respiratory disease or no ultrasonography of both carotid arteries)

1173 subjects with carotid ultrasonography

253 COPD, 920 controls

694 subjects with carotid wall thickening

189 COPD, 505 controls

479 subjects without carotid wall thickening

64 COPD, 415 controls

336 subjects excluded with contraindications for MRI, incompleted or bad quality scan

358 with an interpretable MRI

88 COPD, 270 controls

Intraplaque hemorrhage

Lipid core
1. Carotid wall thickening on ultrasonography

1) Carotid artery wall thickening is more prevalent in COPD. Prevalence increases by COPD severity.

- Control (n=920): 54.9%
- Mild COPD (n=129): 69.0%
- Moderate COPD (n=104): 78.8%
- Severe COPD (n=20): 90.0%

* p <0.005  ** p <0.001
Association between COPD and Carotid artery wall thickening: stratification by smoking status

- **Prevalence carotid wall thickening (%)**
  - Control (n=920)
  - COPD (n=253)

- **Smoking Status**
  - Never smoker (n=395)
  - Former smoker (n=679)
  - Current smoker (n=99)

- **Prevalence**
  - Never smoker: 43.5%
  - Former smoker: 62.9%
  - Current smoker: 50.9%
  - Control: 60.0%
  - COPD: 78.0%

- **Statistical Significance**
  - * p < 0.05
  - ** p < 0.005
  - *** p < 0.001
2. Composition of Carotid artery plaques on MRI

- **Prevalence plaque components (%)**
  - Control (n=270)
  - Mild COPD (n=45)
  - Moderate/severe COPD (n=43)

- **Intraplaque hemorrhage (n=358)**
  - Control: 36.3%
  - Mild COPD: 41.3%
  - Moderate/severe COPD: 37.2%

- **Lipid core (n=358)**
  - Control: 35.2%
  - Mild COPD: 55.6%
  - Moderate/severe COPD: 58.1%

- **Calcification (n=358)**
  - Control: 89.3%
  - Mild COPD: 86.7%
  - Moderate/severe COPD: 81.4%

2) In subjects with carotid wall thickening, COPD is associated with the presence of a lipid core, and therefore of vulnerable plaques.

3. COPD and Carotid plaques: Effect of frequent exacerbations

18.3% frequent COPD exacerbator (of whom 30.5% had COPD hospital admissions)

1) Risk of carotid artery wall thickening

2) Risk of lipid core carotid plaques

3) Frequent COPD exacerbations modify the risk of Carotid wall thickening and lipid core plaques
COPD and Carotid artery plaques: CONCLUSIONS

1) Carotid artery wall thickening is more prevalent in COPD patients than in controls (ultrasonography).

2) COPD is associated with Carotid artery plaques with a lipid core (i.e. vulnerable plaques; MRI).

3) Frequent exacerbations of COPD amplify the risk.

COPD and Carotis plaques: POTENTIAL MECHANISMS

Sin D. & MacNee W., AJRCCM 2013.
COPD and cerebral microbleeds

Prevalence (%) of subjects within group

No COPD (n=645)  
Mild COPD (n=84)  
Moderate/severe COPD (n=81)

* p <0.05

COPD and Cerebral MicroBleeds: location matters

**COPD: conclusion**

**Genetics → Paradigm shift:**
Both impaired lung growth and accelerated decline in lung function contribute to the pathogenesis of COPD.

**Epigenetics:** Dysregulation of micro-RNAs in induced sputum / lungs of smokers and patients with COPD may amplify (perpetuate) airway inflammation and remodeling.
COPD: conclusions

- CXCL13 is increased in COPD and is required for the development of **lymphoid follicles** (local IgA responses).
- COPD is associated with **CNS large and small vessel disease**:
  - Carotid artery wall thickening and lipid core plaques;
  - deep / infratentorial Cerebral Microbleeds.
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Department of Respiratory Medicine
Ghent University, Ghent, Belgium
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