COPD : Year in Review 2024

COPD 원인과 발병 기전

강원대학교병원 호흡기내과 권오범

Pathobiology and Pathophysiology

- Inflammatory changes
- Structural changes
- Airflow obstruction and gas trapping
- Pulmonary gas exchange abnormalities
- Pulmonary hypertension
- Exacerbations
- Multi-morbidity

2024 GOLD REPORT

Proposed taxonomy (etiotypes) for COPD

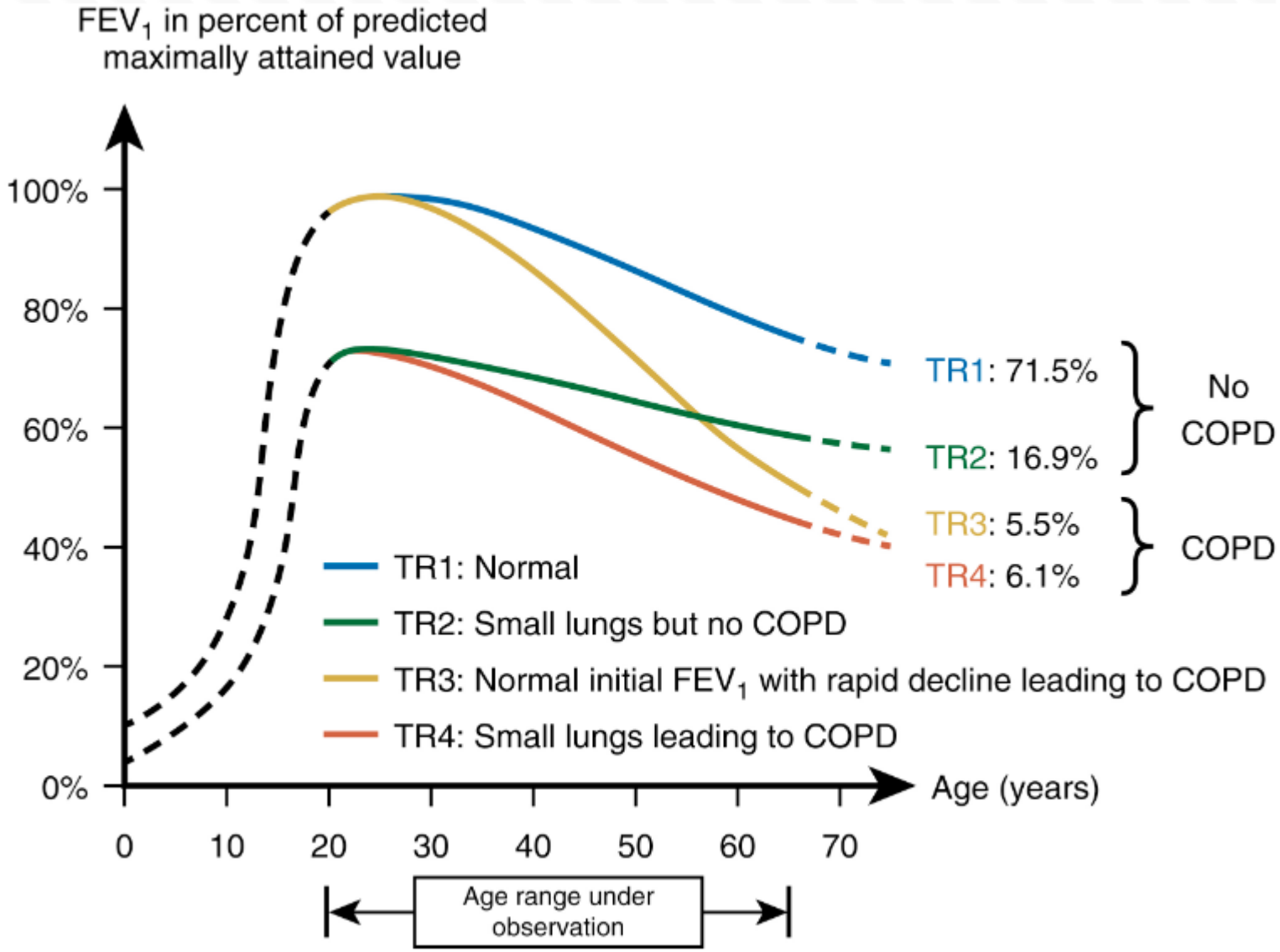
Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or *via* passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD and asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

Adapted from Celli *et al*. [2] and Stolz *et al*. [72].

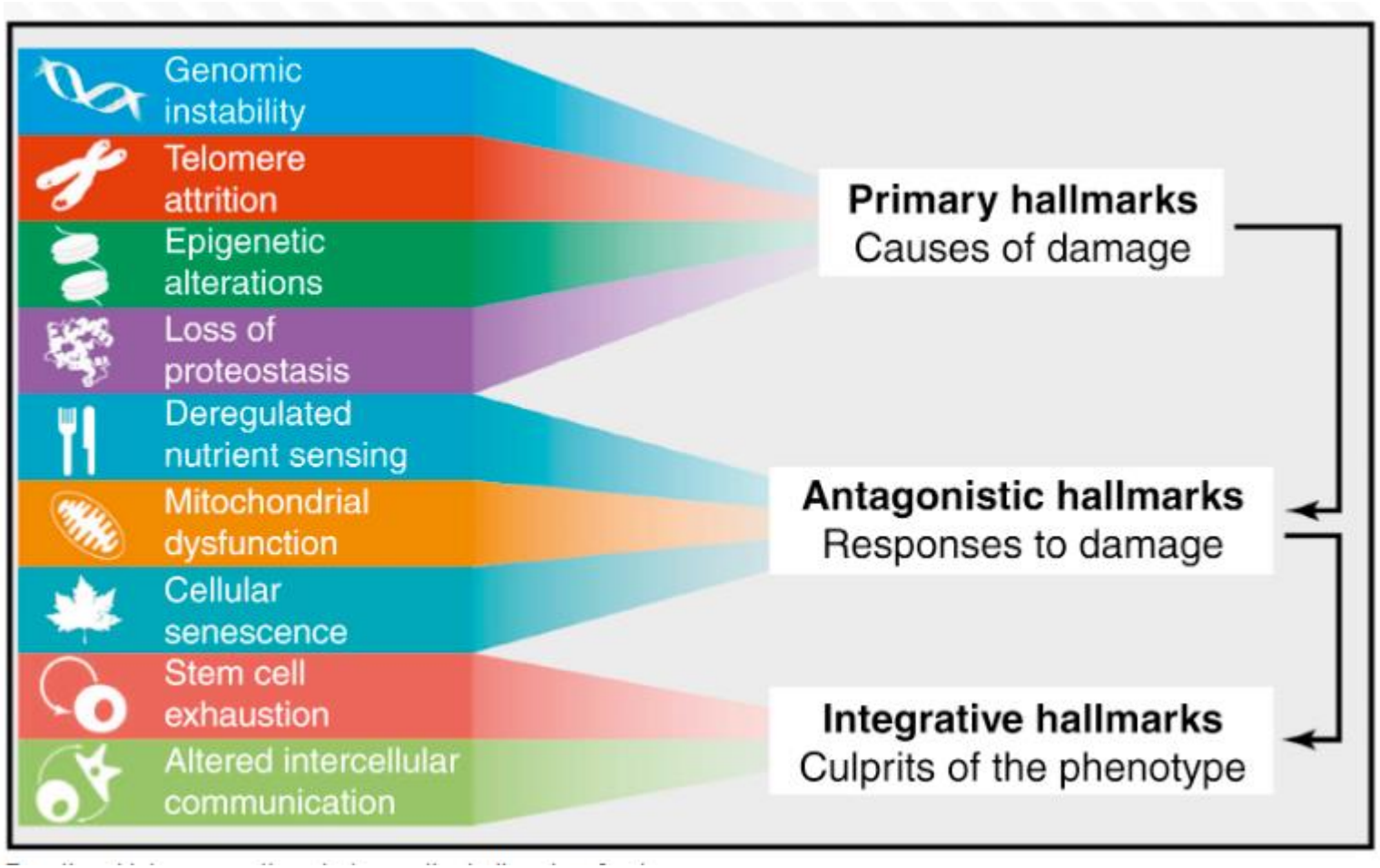
Pathogenesis

- Mechanisms of Oxidant Injury and Antioxidants
- Smoking-induced Epigenetic Reprogramming of the Airway Epithelium
- Small Airway Remodeling and Matrix Damage
- Proteases/Antiproteases
- Innate Cellular Responses
- Mediators of Inflammation and of its Resolution
- Pulmonary Microvascular Changes Induced by Oxidant Injury
- COPD as a Disease of Accelerated Aging
- Adaptive Immune Inflammation and Autoimmunity

Murray & Nadel's Textbook of Respiratory Medicine, Seventh Edition



Lange P, et al. N Eng J Med. 2015



Lopez-Otin C., et al. Cell 2013

- ☐ Inflammatory changes / Structural changes
- ☐ Abnormal lung development
- ☐ Rapid decline
- ☐ Genetic variants

ERJ OPEN RESEARCH
REVIEW
M.E. WECHSLER AND J.M. WELLS

What every clinician should know about inflammation in COPD

Michael E. Wechsler[1] and J. Michael Wells[2]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, USA. [2]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, USA.

Corresponding author: J. Michael Wells (jmwells@uabmc.edu)

Shareable abstract (@ERSpublications)
The cellular nuances of inflammation in COPD can cause heterogeneous presentation and treatment response. The novel therapeutics detailed in this review could advance the field closer to precision medicine. https://bit.ly/4eeEvF0

Cite this article as: Wechsler ME, Wells JM. What every clinician should know about inflammation in COPD. *ERJ Open Res* 2024; 10: 00177-2024 [DOI: 10.1183/23120541.00177-2024].

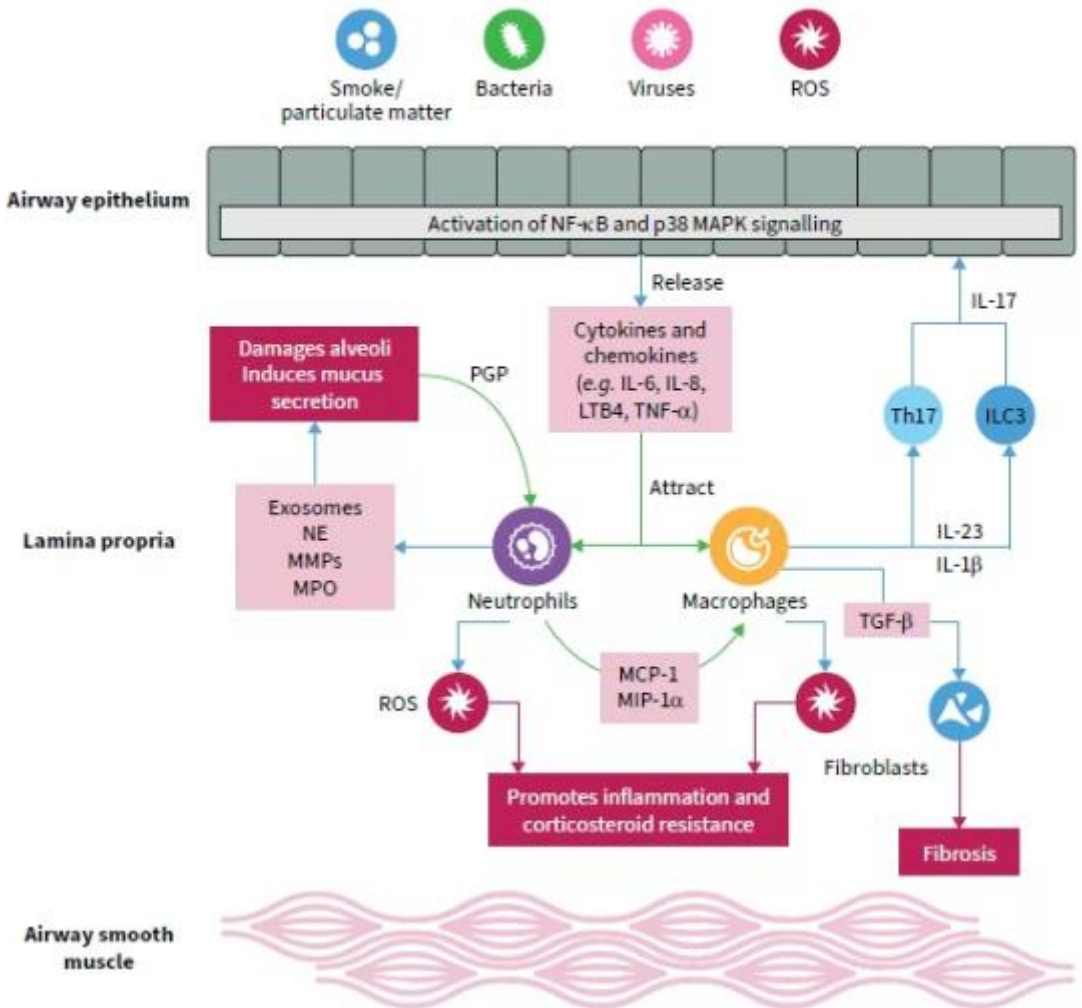
Michael E. Wechsler, et al. ERJ Open Res. 2024

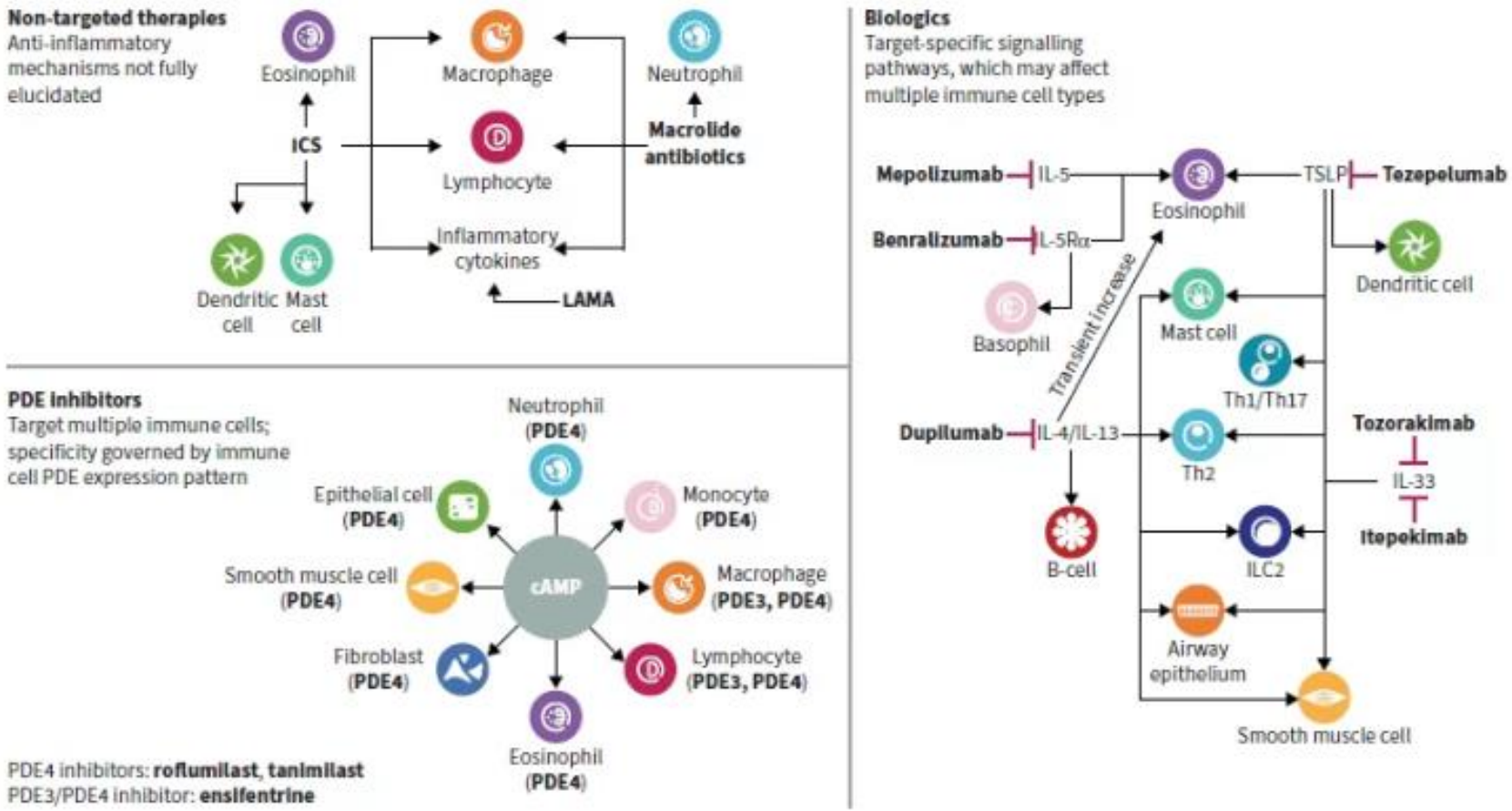
· Exposure to cigarette smoke and other inhaled particles has three major sequelae. – inflammation, protease-antiprotease imbalance and oxidative stress.

· Protease-antiprotease imbalance : Increase in proteases and a decrease in antiprotease activity.

· Pathologic triads – goblet cell hyperplasia, mucus hypersecretion, alveolar wall destruction, and small airway inflammation and fibrosis.

· Structural changes result in increased airway resistance, airway trapping and progressive airflow obstruction.


Smoke/
particulate matter
Bacteria
Viruses
ROS
Airway epithelium
Activation of NF-κB and p38 MAPK signalling
Release
IL-17
Damages alveoli
Induces mucus
secretion
PGP
Cytokines and
chemokines
(e.g. IL-6, IL-8,
LTB4, TNF-α)
Th17
ILC3
Attract
Lamina propria
Exosomes
NE
MMPs
MPO
IL-23
IL-1β
Neutrophils
Macrophages
TGF-β
MCP-1
MIP-1α
ROS
Fibroblasts
Promotes inflammation and
corticosteroid resistance
Fibrosis
Airway smooth
muscle


Non-targeted therapies
Anti-inflammatory mechanisms not fully elucidated
Eosinophil
Macrophage
Neutrophil
ICS
Lymphocyte
Macrolide antibiotics
Inflammatory cytokines
Dendritic cell
Mast cell
LAMA
PDE inhibitors
Target multiple immune cells; specificity governed by immune cell PDE expression pattern
Neutrophil (PDE4)
Epithelial cell (PDE4)
Monocyte (PDE4)
Smooth muscle cell (PDE4)
cAMP
Macrophage (PDE3, PDE4)
Fibroblast (PDE4)
Lymphocyte (PDE3, PDE4)
Eosinophil (PDE4)
PDE4 inhibitors: roflumilast, tanimilast
PDE3/PDE4 inhibitor: ensifentrine
Biologics
Target-specific signalling pathways, which may affect multiple immune cell types
Mepolizumab
IL-5
Eosinophil
TSLP
Tezepelumab
Benralizumab
IL-5Rα
Dendritic cell
Basophil
Transient increase
Mast cell
Th1/Th17
Dupilumab
IL-4/IL-13
Th2
Tozorakimab
IL-33
Itepekimab
B-cell
ILC2
Airway epithelium
Smooth muscle cell

ORIGINAL ARTICLE

Loss of p73 Expression Contributes to Chronic Obstructive Pulmonary Disease

Bradley W. Richmond[1,2,4*], Clayton B. Marshall[3,5*], Jessica B. Blackburn[1,2], Tiffany S. Tufenkjian[1,2], Brian D. Lehmann[3,6], Wei Han[2], Dawn Newcomb[2], Sergey S. Gutor[2], Raphael P. Hunt[1,2], Danielle L. Michell[6], Kasey C. Vickers[6], Vasiliy V. Polosukhin[2], Timothy S. Blackwell[1,2,4‡], and Jennifer A. Pietenpol[3,5‡]

[1]Department of Veterans Affairs Medical Center, Nashville, Tennessee; [2]Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, and [3]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee; and [4]Department of Cell and Developmental Biology, [5]Department of Biochemistry, and [6]Department of Medicine, Vanderbilt University, Nashville, Tennessee

Bradley W. Richmond, et al. Am J Respir Crit Care Med. Jan 2024

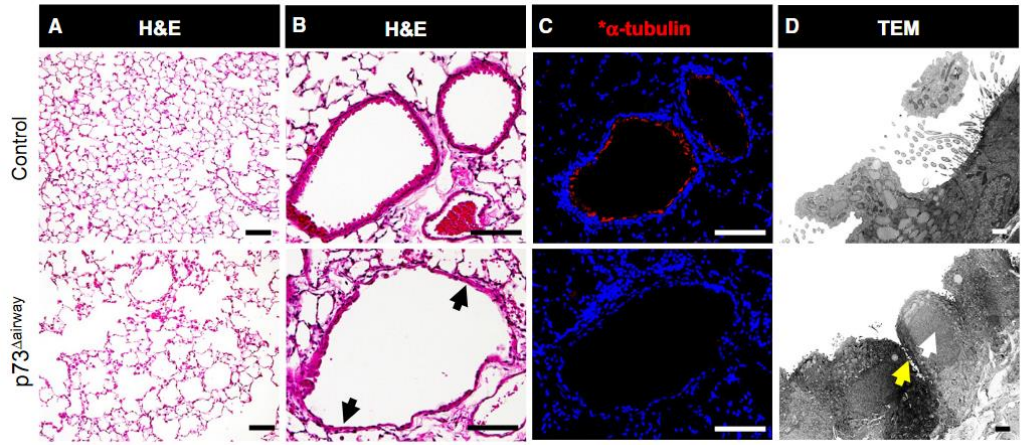
· Loss or impairment of multi-ciliated cells (MCC) may contribute to inadequate mucociliary clearance and mucus plugging in COPD.

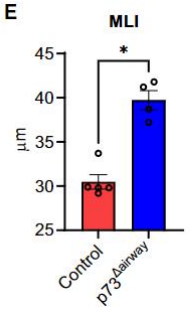
· p73 (tumor protein 73) is expressed in MCCs and is required for MCC development.

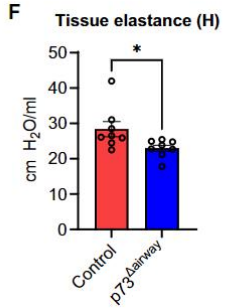
· Loss of p73 in the airways results in loss of MCCs, neutrophilic inflammation and emphysema like lung remodeling.

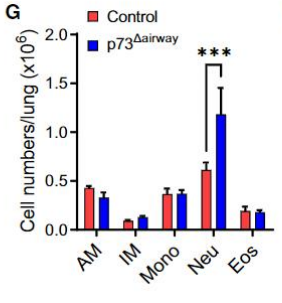
· p73 is suppressed by cigarette smoke and is reduced in the airways of smokers and patients with COPD.

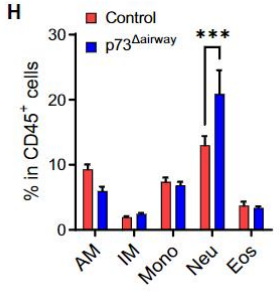
· Loss of secretory cells and secretory cell products is an important contributor to COPD pathology.

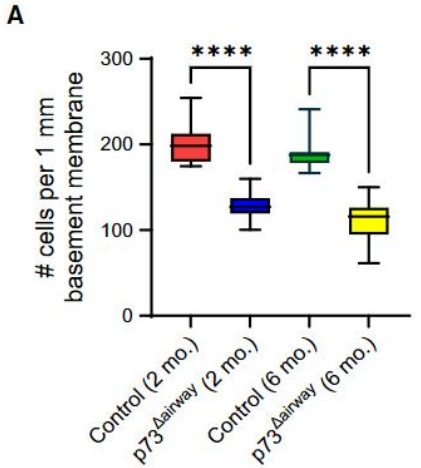

A H&E
B H&E
C *α-tubulin
D TEM
Control
p73Δairway

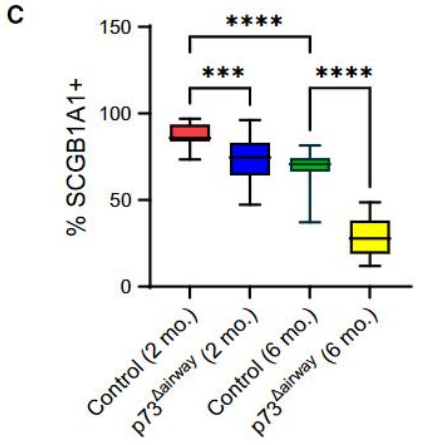

E
MLI
μm
Control
p73Δairway

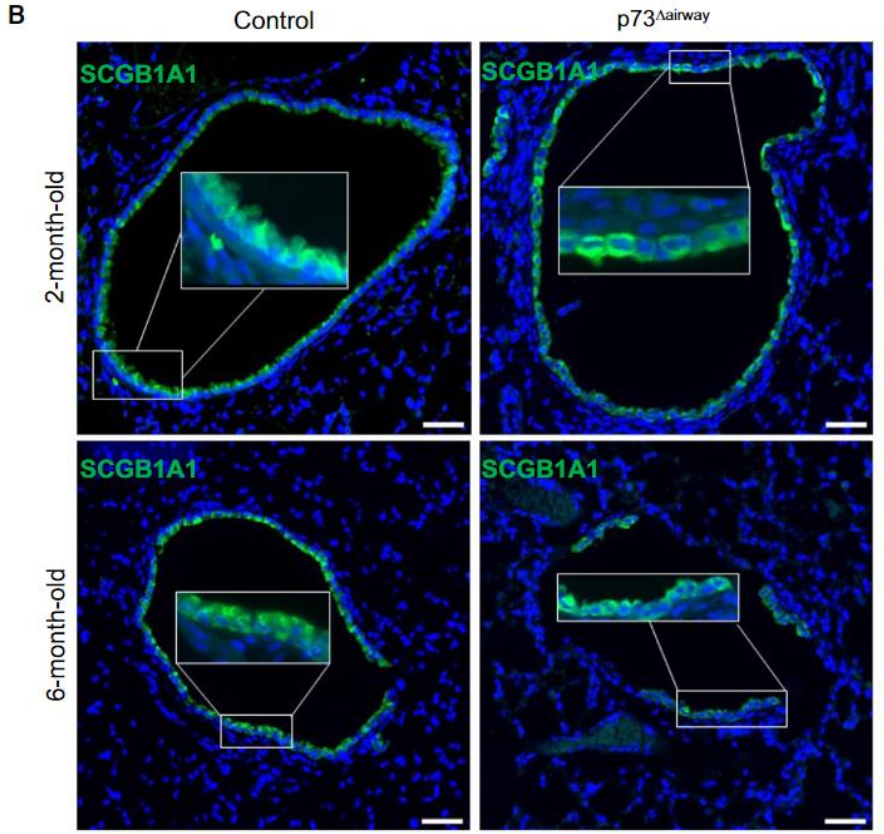

F
Tissue elastance (H)
cm H2O/ml
Control
p73Δairway

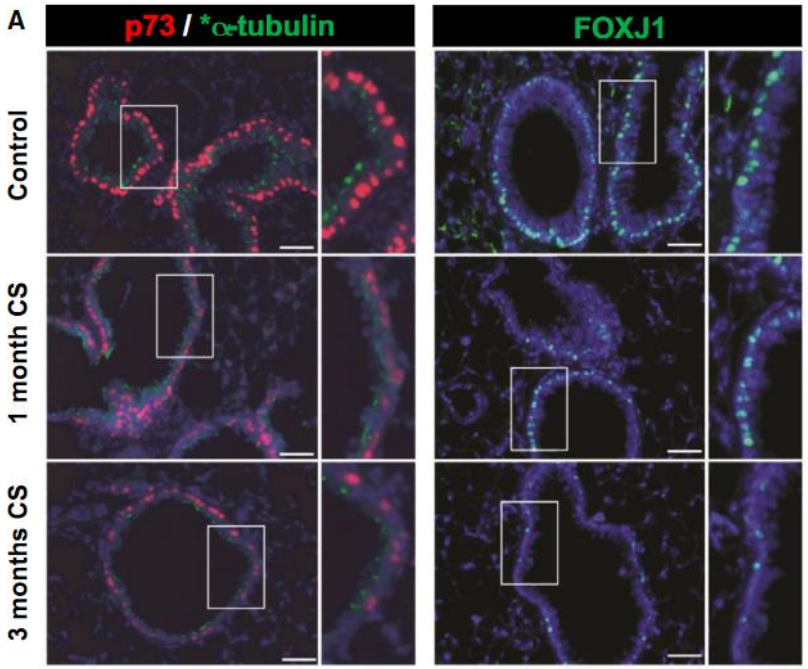

G
Control
p73Δairway
Cell numbers/lung (x10^6)
AM
IM
Mono
Neu
Eos

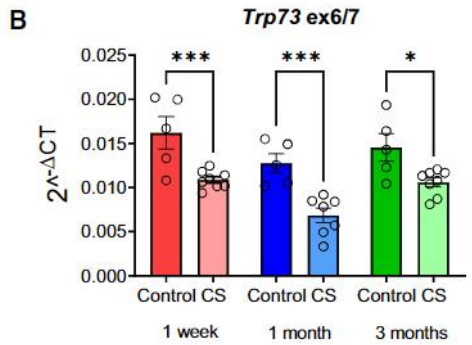

H
Control
p73Δairway
% in CD45+ cells
AM
IM
Mono
Neu
Eos

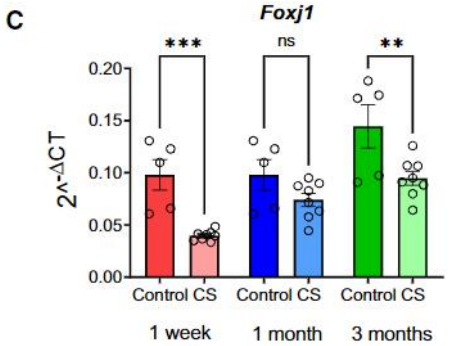

A
cells per 1 mm basement membrane
Control (2 mo.)
p73Δairway (2 mo.)
Control (6 mo.)
p73Δairway (6 mo.)

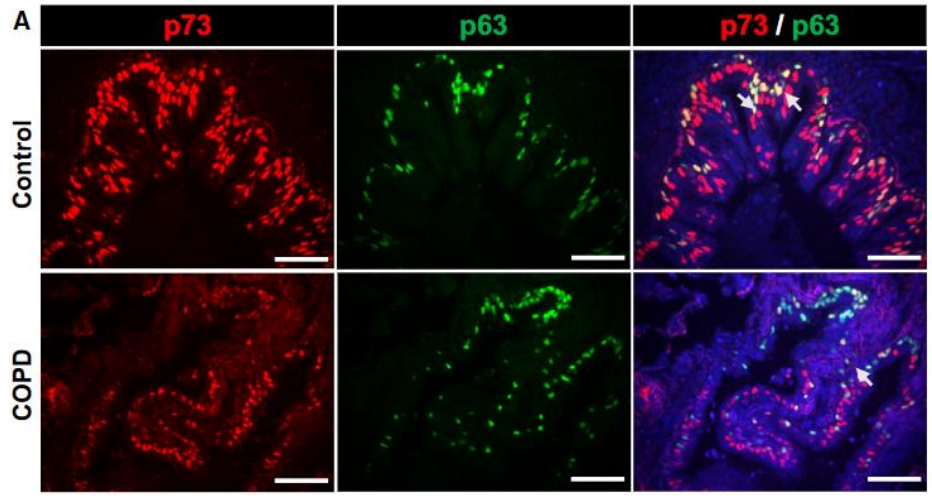

C
% SCGB1A1+
Control (2 mo.)
p73Δairway (2 mo.)
Control (6 mo.)
p73Δairway (6 mo.)

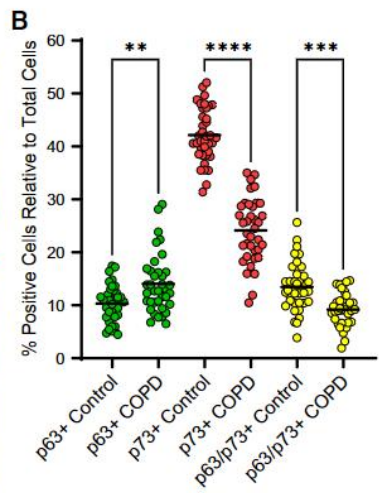

B
Control
p73Δairway
2-month-old
6-month-old
SCGB1A1


A
p73 / *αe-tubulin
FOXJ1
Control
1 month CS
3 months CS


B
Trp73 ex6/7
2^-ΔCT
0.025
0.020
0.015
0.010
0.005
0.000
***
***
*
Control CS
Control CS
Control CS
1 week
1 month
3 months


C
Foxj1
2^-ΔCT
0.20
0.15
0.10
0.05
0.00
***
ns
**
Control CS
Control CS
Control CS
1 week
1 month
3 months


A
p73
p63
p73 / p63
Control
COPD


B
% Positive Cells Relative to Total Cells
60
50
40
30
20
10
0
**
****
***
p63+ Control
p63+ COPD
p73+ Control
p73+ COPD
p63/p73+ Control
p63/p73+ COPD

[COPD Original Research]

CHEST

Silent Airway Mucus Plugs in COPD and Clinical Implications

Sofia K. Mettler, MD, MPH; Hrudaya P. Nath, MD; Scott Grumley, MD; José L. Orejas, MD; Wojciech R. Dolliver, MD; Pietro Nardelli, PhD; Andrew C. Yen, MD; Seth J. Kligerman, MD; Kathleen Jacobs, MD; Padma P. Manapragada, MD; Mostafa Abozeed, MD, PhD; Muhammad Usman Aziz, MD; Mohd Zahid, MD; Asmaa N. Ahmed, MD; Nina L. Terry, MD, JD; Rim Elalami, BS; Ruben San José Estépar, MS; Sushilkumar Sonavane, MD; Ehab Billatos, MD; Wei Wang, PhD; Raúl San José Estépar, PhD; Jeremy B. Richards, MD; Michael H. Cho, MD, MPH; and Alejandro A. Diaz, MD, MPH

Sofia K.Mettler, et al. CHEST. Nov 2024

· Airway mucus plugs are frequently identified on CT scans of patients with COPD with a smoking history without mucus-related symptoms.

· Risk factors of silent mucus plugs were older age, female, and Black race.

· Silent mucus plugs are associated with worse functional, structural, and clinical measures of disease.

· Participants with silent mucus plugs had greater emphysema, and thicker airway walls and higher odds of having severe exacerbations.

TABLE 3] Associations of Silent Mucus Plugs With Measures of Lung Function, Quality of Life, and Structural Changes on Chest Imaging in Multivariable Models

Outcome	Mucus Plug Score Category (No. of Lung Segments With Mucus Plugs)			
	1-2 vs 0		≥ 3 vs 0	
	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Linear regression models				
6-min walk distance, m	−35.88 (−50.17 to −21.58)	< .001	−61.48 (−78.61 to −44.35)	< .001
Resting Spo_2, %	−0.88 (−1.25 to −0.51)	< .001	−0.68 (−1.13 to −0.23)	.003
SGRQ total score	6.48 (4.22 to 8.75)	< .001	10.2 (7.46 to 12.93)	< .001
SGRQ impact score	5.48 (3.42 to 7.53)	< .001	9.01 (6.53 to 11.49)	< .001
SGRQ activity score	8.31 (4.94 to 11.69)	< .001	12.51 (8.43 to 16.58)	< .001
Postbronchodilator FEV_1/FVC	−0.05 (−0.07 to −0.04)	< .001	−0.08 (−0.1 to −0.07)	< .001
Postbronchodilator FEV_1 % predicted	−9.79 (−12.38 to −7.21)	< .001	−16.21 (−19.33 to −13.09)	< .001
Emphysema, % lung volume	4.16 (2.66 to 5.66)	< .001	5.34 (3.52 to 7.17)	< .001
Airway wall thickness (Pi10), mm	0.22 (0.15 to 0.28)	< .001	0.39 (0.31 to 0.47)	< .001
Small airways disease, % lung volume	4.16 (2.72 to 5.6)	< .001	6.53 (4.77 to 8.29)	< .001
Logistic regression models				
Had COPD exacerbation requiring hospitalization in the past 12 mo	1.79 (1.14 to 2.76)	.0101	2.26 (1.38 to 3.62)	< .001

COPD Exposed to Air Pollution

A Path to Understand and Protect a Susceptible Population

Min Hyung Ryu, PhD; Shane Murphy, MD; Madison Hinkley, BSc; and Chris Carlsten, MD, MPH

Min Hyung Ryu, et al. CHEST, Apr 2024

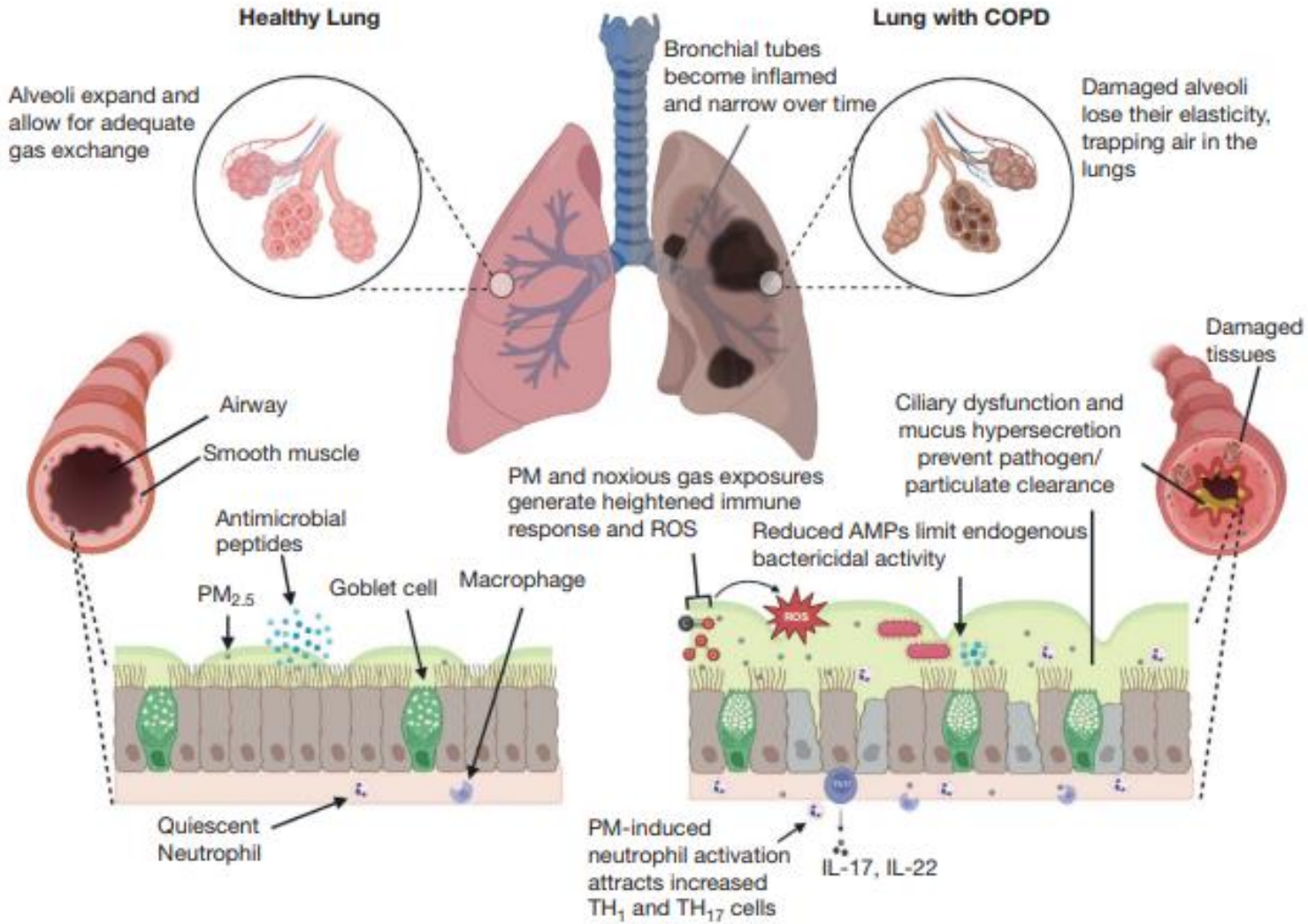
· Increase of $PM_{2.5}$ and NO_2 concentration increases the risk of COPD hospitalization and ED visits.

· Long term exposure to air pollution ($PM_{2.5}$, NO_2 and ozone) was positively associated with a higher incidence of COPD.

· Exposure to diesel exhaust was associated with an increase in neutrophil extracellular traps (NETs).

· Higher level of daily $PM_{2.5}$ was associated with increased inflammation biomarkers.

· Airway wall thickening and loss of parenchyma elasticity resulted in airflow limitation .


Healthy Lung
Lung with COPD
Alveoli expand and allow for adequate gas exchange
Bronchial tubes become inflamed and narrow over time
Damaged alveoli lose their elasticity, trapping air in the lungs
Damaged tissues
Airway
Smooth muscle
Antimicrobial peptides
$PM_{2.5}$
Goblet cell
Macrophage
PM and noxious gas exposures generate heightened immune response and ROS
Ciliary dysfunction and mucus hypersecretion prevent pathogen/ particulate clearance
Reduced AMPs limit endogenous bactericidal activity
ROS
Quiescent Neutrophil
PM-induced neutrophil activation attracts increased TH_1 and TH_{17} cells
IL-17, IL-22

ORIGINAL ARTICLE

Accelerated Lung Function Decline and Mucus–Microbe Evolution in Chronic Obstructive Pulmonary Disease

Oliver W. Meldrum[1], Gavin C. Donaldson[2†], Jayanth Kumar Narayana[1], Fransiskus Xaverius Ivan[1], Tavleen K. Jaggi[1], Micheál Mac Aogáin[1], Lydia J. Finney[2], James P. Allinson[2,3], Jadwiga A. Wedzicha[1,2], and Sanjay H. Chotirmall[1,4]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [2]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [3]Royal Brompton Hospital, London, United Kingdom; and [4]Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore

Oliver W. Meldrum, et al. Am J Respir Crit Care Med. Aug 2024

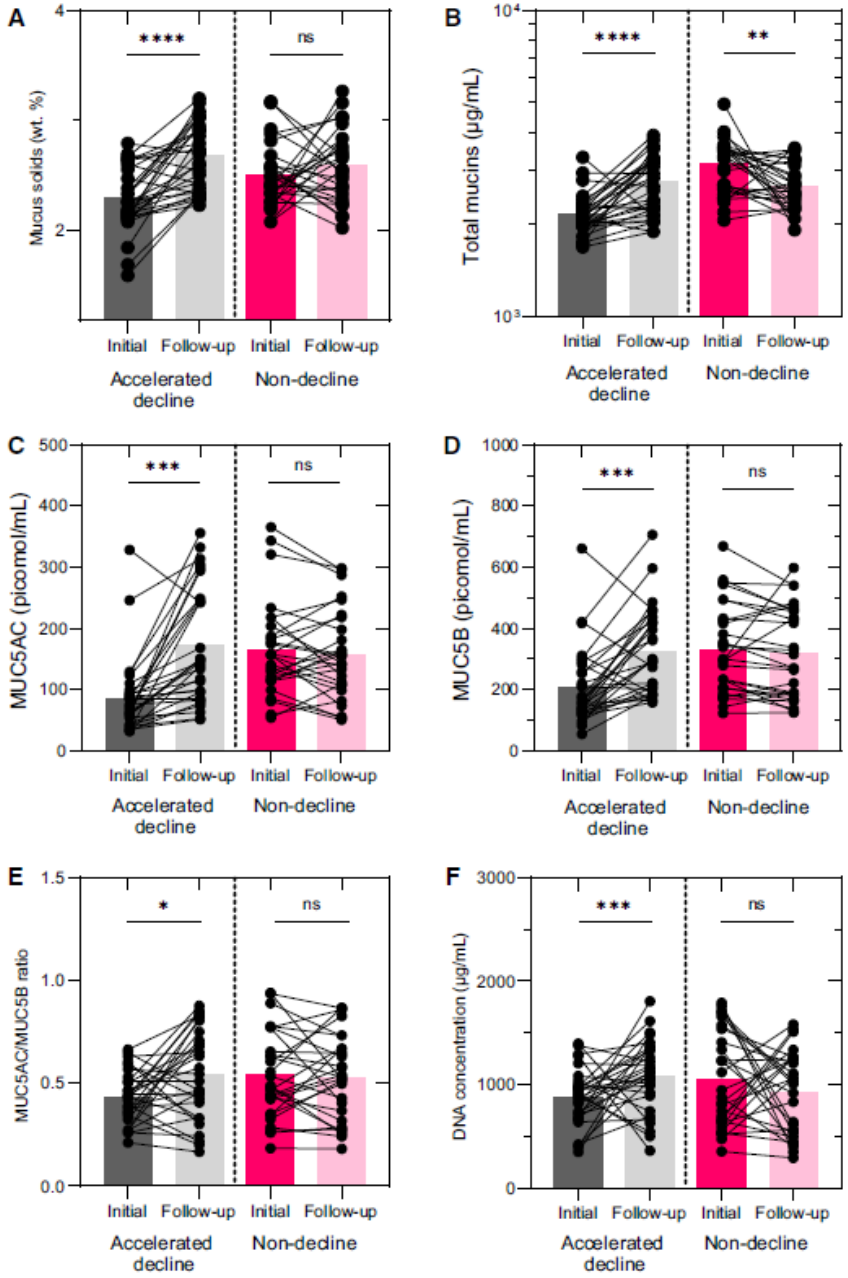
· Mucus hypersecretion and altered inflammation predispose to microbial colonization, infection and exacerbations in COPD.

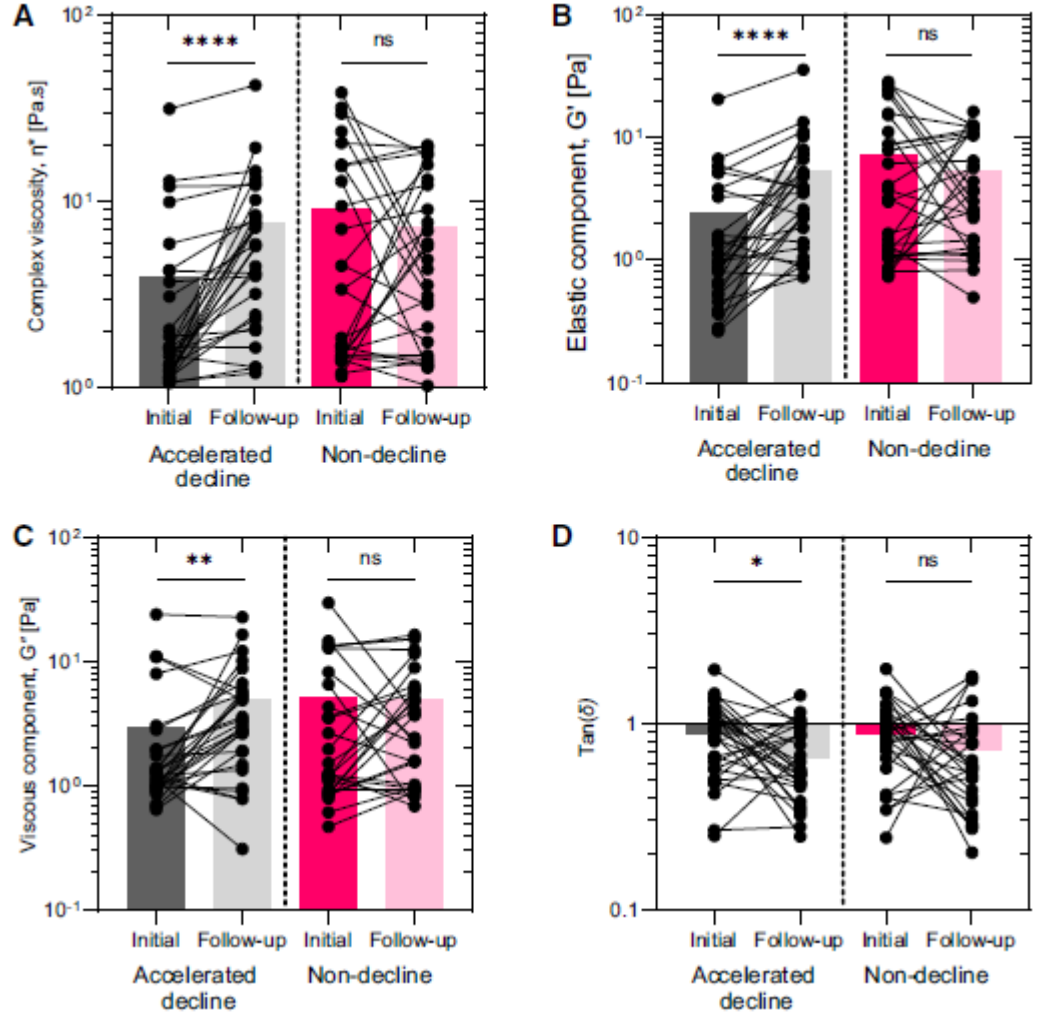
· MUC5AC (mucin 5AC) and MUC5B (mucin 5B) are elevated in COPD.

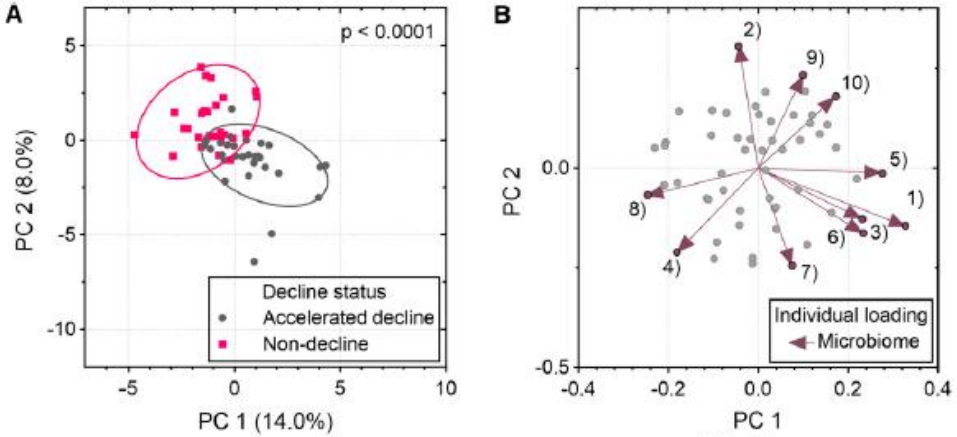
· Increases in percentage mucus solids, total mucin concentration, MUC5AC, MUC5B concentration and MUC5AC/MUC5B ratio was observed in the accelerated decline group. None-decline group had much higher baseline values.

· *Achromobacter*, *Klebsiella* and *Bordetalla* were increased in the accelerated decline group. *Gemella* and *Veillonella* were elevated in the non-decline group.

· Close links between mucus and microbes in the COPD airway were observed.

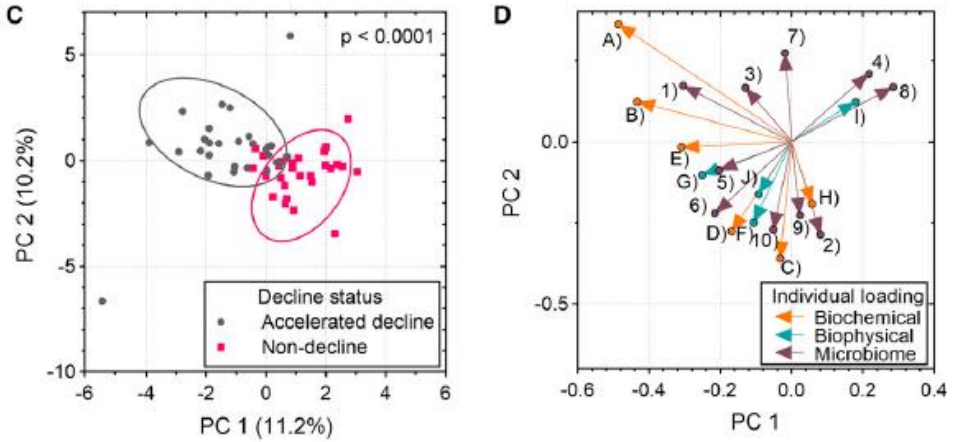

A
Mucus solids (wt. %)
****
ns
B
Total mucins (μg/mL)
****
**
C
MUC5AC (picomol/mL)
***
ns
D
MUC5B (picomol/mL)
***
ns
E
MUC5AC/MUC5B ratio
*
ns
F
DNA concentration (μg/mL)
***
ns
Initial
Follow-up
Accelerated decline
Non-decline


A
Complex viscosity, η* [Pa.s]
****
ns
B
Elastic component, G' [Pa]
****
ns
C
Viscous component, G'' [Pa]
**
ns
D
Tan(δ)
*
ns
Initial
Follow-up
Accelerated decline
Non-decline



Microbiome

1) *Achromobacter*
2) *Providencia*
3) *Klebsiella*
4) *Veillonella*
5) *Alcaligenes*
6) *Bordetella*
7) *Parvimonas*
8) *Gemella*
9) *Brevundimonas*
10) *Delftia*

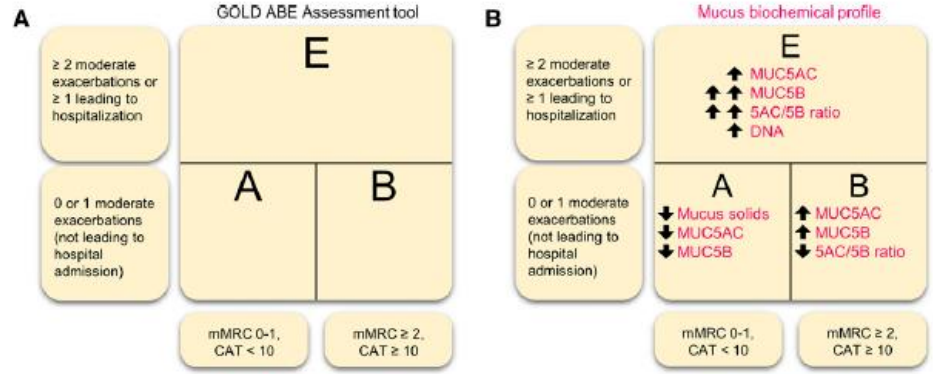


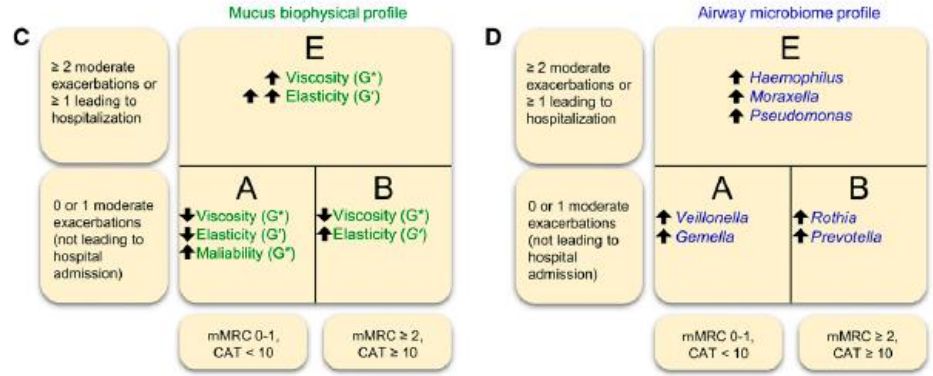
Microbiome

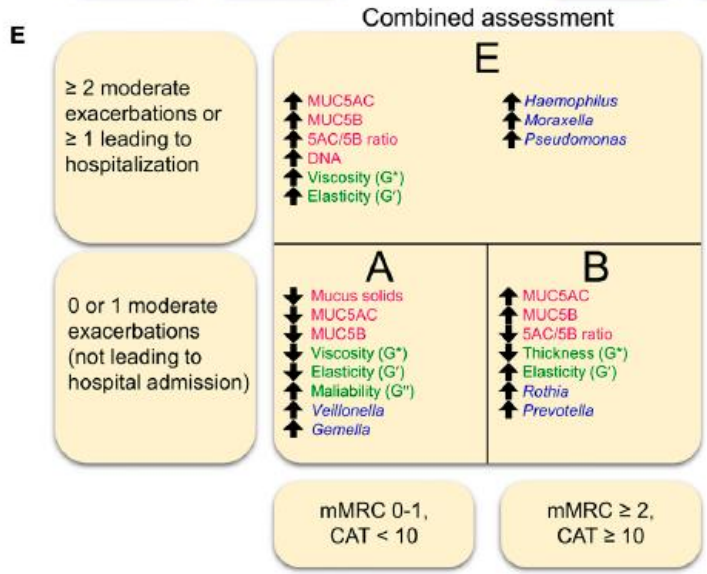
1) *Achromobacter*
2) *Providencia*
3) *Klebsiella*
4) *Veillonella*
5) *Alcaligenes*
6) *Bordetella*
7) *Parvimonas*
8) *Gemella*
9) *Brevundimonas*
10) *Delftia*

Mucus profile

A) MUC5B
B) MUC5AC
C) DNA
D) Mucus solids
E) Total mucins
F) Elastic component
G) Complex viscosity
H) 5AC/5B ratio
I) *tanδ*
J) Viscous component







OPEN ACCESS

Original research

Lower airway microbiota in COPD and healthy controls

Solveig Tangedal ,[1,2] Rune Nielsen,[1,2] Marianne Aanerud,[1,2] Christine Drengenes,[2] Gunnar R Husebø,[1] Sverre Lehmann,[1,2] Kristel S Knudsen,[1] Pieter S Hiemstra ,[3] Tomas ML Eagan[1,2]

Tangedal S, et al. Throax Feb 2024

· Lower airway microbiota has been suggested to contribute to the development and progression of several lung diseases.

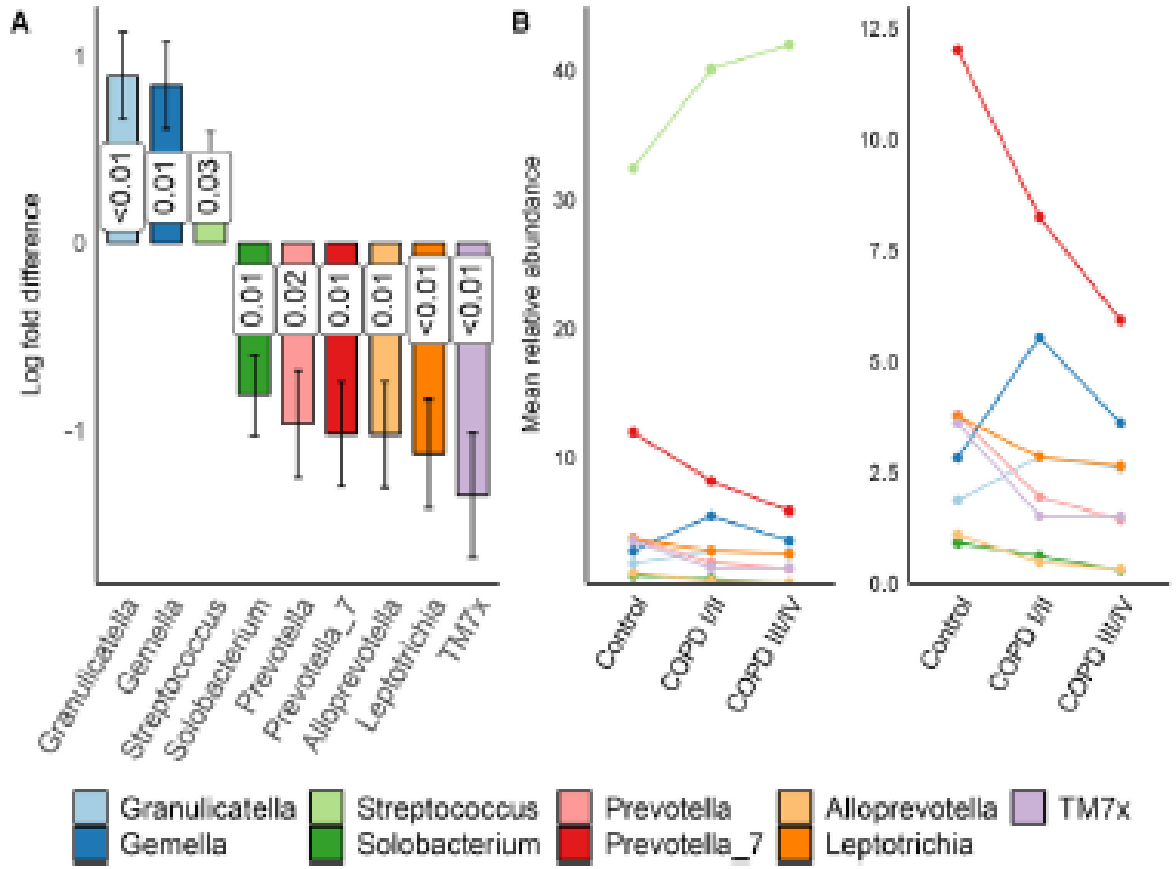
· Bronchoalveolar lavages samples were paired-end sequenced with the Illuimina MiseQ System.

· Alpha-diversity was lower in COPD compared with controls. Beta-diversity did not differ significantly between patients with COPD and controls.

· *Firmicutes* were enriched in patients with COPD while *Bacteroidota* were enriched in controls.

· The lower airway microbiota is equal in richness in patients with COPD to controls, but less even.

· Remodeling in COPD airways can create an environment in which certain bacteria thrive. Overgrowth of pathogenic bacteria could contribute to the remodeling seen in COPD.


A
B
Log fold difference
Mean relative abundance
<0.01
0.01
0.03
0.01
0.02
0.01
0.01
<0.01
<0.01
Granulicatella
Gemella
Streptococcus
Solobacterium
Prevotella
Prevotella_7
Alloprevotella
Leptotrichia
TM7x
Control
COPD I/II
COPD III/IV
Granulicatella
Gemella
Streptococcus
Solobacterium
Prevotella
Prevotella_7
Alloprevotella
Leptotrichia
TM7x

Genetic and Epigenetic Associations with Pre–Chronic Obstructive Pulmonary Disease Lung Function Trajectories

David J. Martino[1], Dinh S. Bui[2], Shuai Li[2,3,4,5], Sabrina Idrose[2], Jennifer Perret[2], Adrian J. Lowe[2,5], Caroline J. Lodge[2,5], Gayan Bowatte[2], Yuben Moodley[6], Paul S. Thomas[7], Graeme Zosky[8], Philip M. Hansbro[9], John W. Holloway[10], Cecilie Svanes[11,12], Rosa Faner[13,14,15], Eugene H. Walters[2,16,17]*, and Shaymali C. Dharmage[2,5]*

[1]Wal-yan Respiratory Research Centre, Telethon Kids Institute, University of Western Australia, West Perth, Western Australia, Australia; [2]Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia; [3]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [4]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia; [5]Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia; [6]Department of Respiratory Medicine, Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [7]Respiratory Medicine, Prince of Wales Hospital and Prince of Wales Clinical School, University of New South Wales, Randwick, New South Wales, Australia; [8]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; [9]Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, New South Wales, Australia; [10]Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [11]Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [12]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway; [13]Immunology Unit, Biomedicine Department, University of Barcelona, Barcelona, Spain; [14]Institut d'Investigacions Biomediques August Pi i Sunyer–Fundació Clinic Recerca, Barcelona, Spain; [15]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Madrid, Spain; [16]School of Medicine, University of Tasmania, Hobart, Tasmania, Australia; and [17]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia

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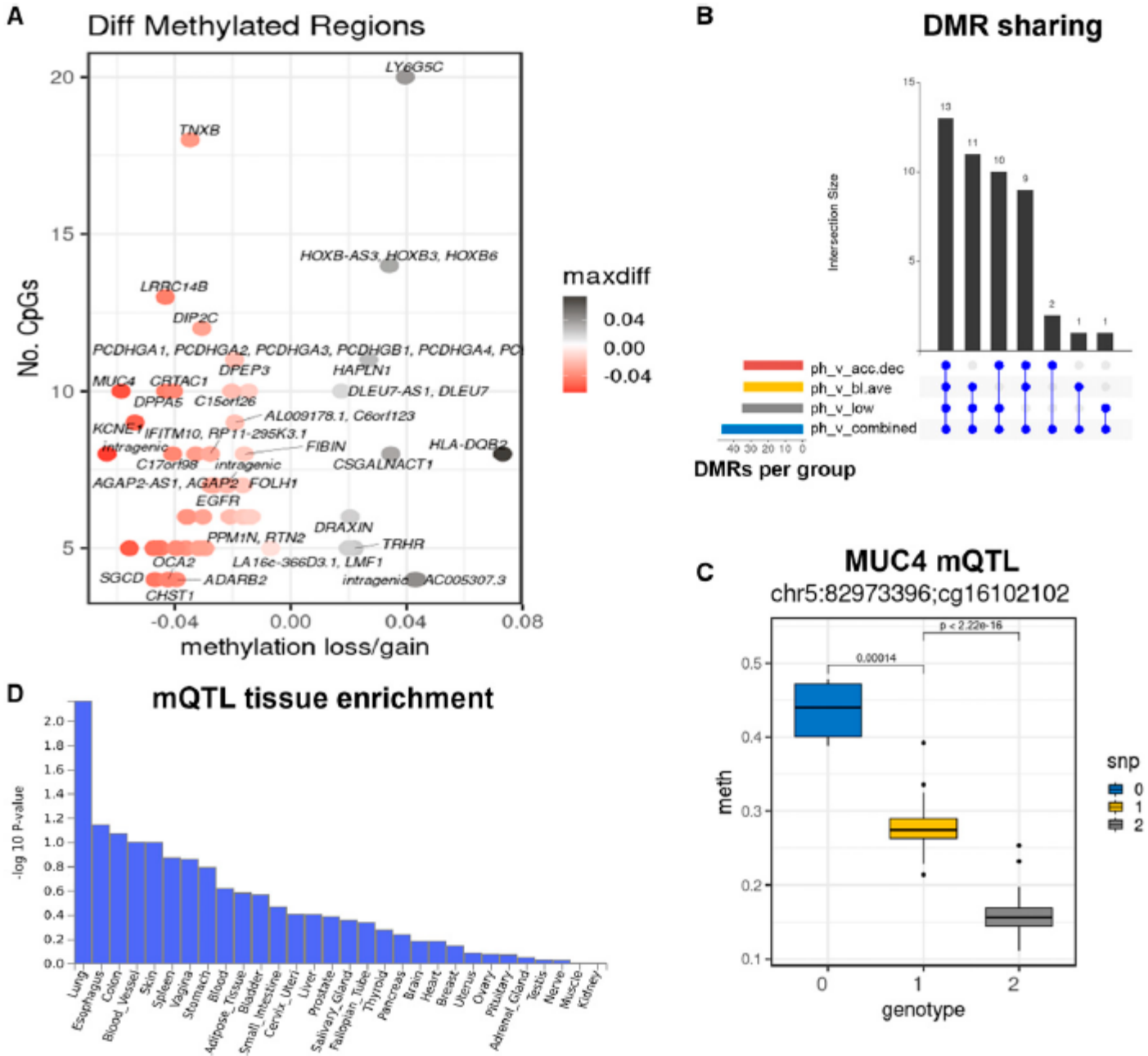
- Quantified 787,111 DNA methylation markers and 4,456,571 SNPs.

- High-risk trajectories were 1) early below-average lung function 2) persistently low and 3) early below-average lung function with accelerated decline.

- DNA methylation changes at 55 differentially methylated regions (DMRs) containing 73 unique genes and 6 non-coding regions between the control group and the high-risk trajectory group.

- Current COPD or current asthma explained 17-30% of methylation differences across the DMRs.

- Molecular risk factors are unique across different lifetime lung function trajectories.


A
Diff Methylated Regions
No. CpGs
methylation loss/gain
maxdiff
0.04
0.00
-0.04
LY6G5C
TNXB
HOXB-AS3, HOXB3, HOXB6
LRRC14B
DIP2C
PCDHGA1, PCDHGA2, PCDHGA3, PCDHGB1, PCDHGA4, PC
DPEP3
HAPLN1
MUC4
CRTAC1
DLEU7-AS1, DLEU7
DPPA5
C15orf26
AL009178.1, C6orf123
KCNE1
IFITM10, RP11-295K3.1
intragenic
FIBIN
HLA-DQB2
C17orf98
intragenic
CSGALNACT1
AGAP2-AS1, AGAP2
FOLH1
EGFR
DRAXIN
PPM1N, RTN2
TRHR
OCA2
LA16c-366D3.1, LMF1
SGCD
ADARB2
intragenic
AC005307.3
CHST1
B
DMR sharing
Intersection Size
ph_v_acc.dec
ph_v_bl.ave
ph_v_low
ph_v_combined
DMRs per group
C
MUC4 mQTL
chr5:82973396;cg16102102
p < 2.22e-16
0.00014
meth
genotype
snp
0
1
2
D
mQTL tissue enrichment
-log 10 P-value
Lung
Esophagus
Colon
Blood_Vessel
Skin
Spleen
Vagina
Stomach
Blood
Adipose_Tissue
Bladder
Small_Intestine
Cervix_Uteri
Liver
Prostate
Salivary_Gland
Fallopian_Tube
Thyroid
Pancreas
Brain
Heart
Breast
Uterus
Ovary
Pituitary
Adrenal_Gland
Testis
Nerve
Muscle
Kidney

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JKMS

Original Article

Respiratory Diseases & Critical Care Medicine

Check for updates

Genome-Wide Association Analysis of Rapid Decline in Lung Function: Analysis From the Korean Genome and Epidemiology Study

Sang Hyuk Kim,[1] **Hyun Lee**,[2] **Yong Suk Jo**,[3] **Jaeeun Yoo**,[4] **and Joon Young Choi**[5]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Dongguk University Gyeongju Hospital, Dongguk University College of Medicine, Gyeongju, Korea
[2]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4]Department of Laboratory Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[5]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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· A genome-wide association analysis of the rapid decline in FEV_1 (≥60mL/year) identified 15 associated signals.

· Among the 15 nucleotide variants, rs9833533 and rs1496255 have been previously reported to be associated with lung function development.

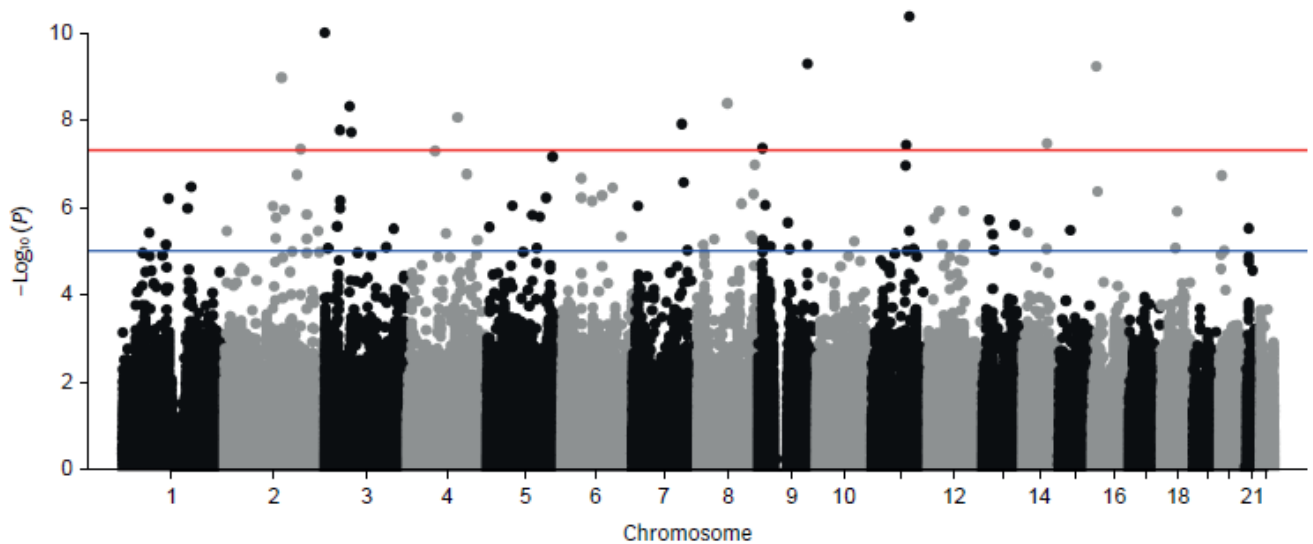
· rs16951883 was the most significant SNP associated with rapid decline in FEV_1 among never smokers.

· rs10959478 was the most significant SNP among ever smokers.

Table 2. Identified SNPs from the GWAS analysis

Rank	SNP	CHR	BP	Risk allele	No.	aOR	*P*	Reported gene and trait
1	rs41476549	11	90617150	C	5,966	2.43	4.35×10^{-11}	No results found
2	rs6805861	3	440476	T	5,985	2.45	1.01×10^{-10}	No results found
3	rs16906215	9	119586079	G	6,137	2.51	5.24×10^{-10}	No results found
4	rs16951883	16	10226280	C	5,982	2.79	6.05×10^{-10}	ATF7IP2, RN7SL493P: Subscapular skinfold thickness[12]
5	rs16840064	2	138479321	A	5,997	2.40	1.09×10^{-9}	No results found
6	rs1481797	8	72168704	C	5,945	2.15	4.24×10^{-9}	No results found
7	rs9833533	3	60543293	A	6,079	2.30	4.91×10^{-9}	FHIT: Lung function (maximal voluntary ventilation)[8]
8	rs1496255	4	121823884	G	6,058	2.43	8.93×10^{-9}	PRDM5, MAD2L1-DT: Lung function (maximal voluntary ventilation), Lung function (forced expiratory volume in 1 second), Lung function (forced vital capacity)[8]
9	rs798912	7	120695721	C	6,120	2.53	1.26×10^{-8}	No results found
10	rs17248901	3	36622465	C	6,043	2.15	1.73×10^{-8}	NBPF21P, STAC: Subscapular skinfold thickness[12]
11	rs17071575	3	64788208	A	6,037	2.05	1.93×10^{-8}	No results found
12	rs17109716	14	79206598	A	6,093	2.10	3.52×10^{-8}	No results found
13	rs17145229	11	82862073	C	6,029	2.30	3.82×10^{-8}	No results found
14	rs10959478	9	11032142	C	6,153	3.07	4.52×10^{-8}	No results found
15	rs1350110	2	184836188	A	6,114	2.24	4.73×10^{-8}	No results found
Never smoker								
1	rs16951883	16	10226280	C	3,517	3.24	5.87×10^{-8}	ATF7IP2, RN7SL493P: Subscapular skinfold thickness[12]
2	rs41476549	11	90617150	C	3,500	2.58	3.99×10^{-7}	No results found
3	rs16840064	2	138479321	A	3,532	2.60	2.10×10^{-6}	No results found
4	rs1350110	2	184836188	A	3,604	2.54	2.14×10^{-6}	No results found
Ever smoker								
1	rs10959478	9	11032142	C	2,527	4.74	8.27×10^{-7}	No results found
2	rs6805861	3	440476	T	2,462	2.55	1.60×10^{-6}	No results found
3	rs9833533	3	60543293	A	2,488	2.66	1.77×10^{-6}	FHIT: Lung function (maximal voluntary ventilation)[8]
4	rs16906215	9	119586079	G	2,526	2.73	2.83×10^{-6}	No results found

Smoking was excluded in the adjusted for the subgroup analysis.
SNP – single-nucleotide polymorphism, GWAS – genome-wide association study, CHR – chromosome, BP – base pair, aOR – adjusted odds ratio.



Original Article

Clonal Hematopoiesis of Indeterminate Potential Is Associated with Current Smoking Status and History of Exacerbation in Patients with Chronic Obstructive Pulmonary Disease

Jung-Kyu Lee, M.D.[1], Hongyul An, M.D.[2], Youngil Koh, M.D., Ph.D.[2,3] and Chang-Hoon Lee, M.D., Ph.D.[4]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, [2]Genome Opinion Inc., Seoul, Divisions of [3]Hematology and Oncology, [4]Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

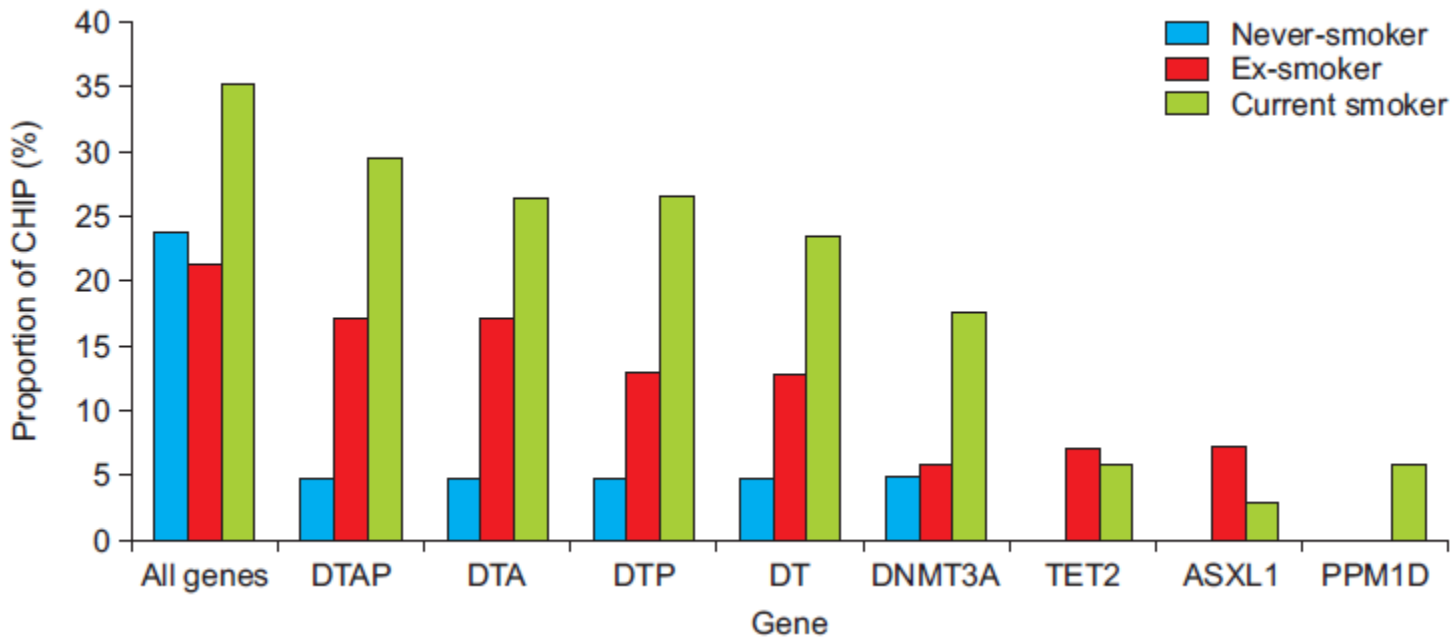
Jung-Kyu Lee, et al. Tuberc Respir Dis. Feb 2024

· Clonal hematopoiesis of indeterminate potential (CHIP) : somatic mutations in hematopoietic stem cells -> clonal outgrowth of a mutant population of blood cells without hematologic malignancy.

· Higher prevalence of CHIP was observed in COPD patients compared to non-COPD patients.

· CHIP in the DTP and DNMT3A genes were significantly associated with current smoking.

· Smoking has a causal association with mosaic chromosomal alterations and this can lead to the subsequent accumulation of other gene mutations.


Never-smoker
Ex-smoker
Current smoker
Proportion of CHIP (%)
40
35
30
25
20
15
10
5
0
All genes
DTAP
DTA
DTP
DT
DNMT3A
TET2
ASXL1
PPM1D
Gene

Summary

- Inflammatory changes
  - loss of p73 expression
  - silent mucus plug

- Microbiome
  - Microbiome diversity and composition

- Genetics
  - DNA methylation, SNP and CHIP

☐ Inflammatory changes / Structural changes

☐ Abnormal lung development

☐ Rapid decline

☐ Genetic variants