Supporting information

Methods

Study populations

Between March 2007 and November 2016, 241 patients with stable COPD aged between 26 and 82 years and without concurrent asthma were included in the COBRA cohort, a multicenter prospective cohort that recruits patients with asthma and COPD from 15 University Pulmonology Departments in France (S1 Table) [S1,S2]. COPD patients were considered stable since they did not report any exacerbation, as defined below, within the month before each visit.

Patients were managed according to the best standard care of tertiary hospital's outpatient clinics in each centre participating in the study. This cohort was approved by the CPP Ile-de-France I Ethics Committee (n° 09-11962) and all subjects gave their written informed consent before being enrolled.

During the first visit (inclusion), demographic data, smoking history, peripheral cell counts, number of exacerbations, of unscheduled hospital visits and hospitalizations for COPD in the previous year, symptoms (cough and wheezing), pulmonary and extra-pulmonary co-morbidities and baseline medications were recorded in a validated standardized folder (S1 Table).

In addition, all patients underwent spirometry, and forced expiratory volume in one sec (FEV_1) and forced vital capacity (FVC) were monitored before and after the inhalation of 400 µg of salbutamol. Functional Residual Capacity (FRC), Residual Volume (RV) and Total Lung Capacity (TLC) were also determined. Lung emphysema was assessed by computed tomography (CT) and by the measurement of transfer

factor of the lung for carbon monoxide (DLCO), the latter correlating well with CT-determined emphysema for all Global Initiative for Obstructive Lung Disease (GOLD) stages [S3,S4].

COPD severity was graded into stage I (22.7%), II (36.5 %), III (22.3%) and IV (18.5%), following GOLD [S5] (S1 Table). Most of the COPD patients were former smokers (61.8%) and they showed airflow obstruction with mean values of pre- and post-bronchodilator FEV_1 lower than 70% of predicted and of pre- and post-bronchodilator FEV_1 to FVC ratio lower than 60%. Approximately 60% of the patients had fixed airflow obstruction, with values of post-bronchodilator FEV_1/FVC lower than 70% [S5] and 38.2% of them exhibited emphysema on CT scan. Around 40% of the patients experienced cough and 13.7 % had wheezing.

The majority of the patients (between 62.3 and 69.1%) were treated with short- and long-acting β2-agonists (SABA and LABA, respectively), long-acting muscarinic antagonists (LAMA, 52.4%) and inhaled corticosteroids (ICS, 52.8%). These drugs were administered alone, or in combination (LABA + LAMA, or LABA + ICS + LAMA) (S1 Table).

As previously reported [S6-S9], principal co-morbidities were of cardiovascular origin (42.7%), but also metabolic disorders, such as dyslipidemia (24.1%) and diabetes (11.6%). A sub-group of COPD patients also manifested allergic rhinitis and sinusitis (15.8 and 11.2%, respectively) and gastro-esophageal reflux (29%). Because of the high frequency of cardiovascular disorders and dyslipidemia, 34.5% of the patients were treated with anti-hypertensive drugs and 24.2% with statins. The proportion of patients adhering to treatments was of more than 90% (S1Table).

Exacerbations were defined as “acute worsening of respiratory symptoms that results in additional therapy”. Patients were classified as mild, if they were treated with SABA only, moderate if they were treated with LABA plus antibiotics and/or oral corticosteroids (OCS) bursts, or severe, if the patient visits the emergency room, or requires hospitalization [S5]. Unscheduled visits were recorded, either to the emergency department or to patient’s usual general practitioner.

Peripheral venous blood was obtained in each patient and total and differential leukocyte counts (in numbers per mm^3), levels of hemoglobin (in g per decilitre) and C reactive protein (CRP, in mg per Litre) were assessed. Median numbers of total and differential blood leukocytes were in a normal range and 16.4 % of patients showed numbers of eosinophils ≥ 300 per µL [S10] and 75.9 % had values of CRP ≥ 3 mg/Litre (S1 Table) [S11].

Serum aliquots (250 µL) were prepared and stored at -80°C at the Biological Resources Centre of the Bichat Hospital in Paris (Dr. Sarah Tubiana) for the determination of proteomic profile by SOMAscan. All samples were tracked through a dedicated database.

The evolution in the clinical parameters and in proteomic profiles was also assessed in 163 COPD patients, out of the 241 initially included, since they provided one satisfactory follow-up visit and blood sampling (S1 Table). The time elapsing from the 1^{st} (inclusion) and the 2^{nd} visit was of 7.5 ± 6.6 months (mean ± SD).

SOMAscan data obtained in the COBRA cohort were validated in a separate series of 47 COPD patients originating from the Melbourne Longitudinal COPD Cohort (MLCC) cohort, that was established to study the etiology of frequent exacerbators in

a community setting [S12] (Table S2). These 47 COPD subjects were more severe and symptomatic in comparison to those from the COBRA cohort. Indeed, 61.7% and 40.8% of patients in the MLCC and COBRA cohorts, respectively, belonged to GOLD 3-4 stages (p=0.01, Fisher exact test), 82.6% and 40.2%, respectively experienced cough, 97.7% and 53.0 % of patients were treated with LAMA, 91.5% and 52.8% received long-term ICS and 57.4% and 15.5 % were on oxygen therapy (all p<0.0001) (S1 and S2 Tables). Airflow obstruction was also more severe in MLCC than in COBRA cohort and the prevalence of emphysema was higher in the former than in the latter cohort (94.0 % and 38.2%, respectively, p<0.0001, S2 Table).

Serum samples were also prepared from peripheral blood of n=50 non-COPD, non-asthmatic healthy volunteers who served as controls. These subjects were anonymously enrolled in the AstraZeneca Research Specimen Collection Program and they provided signed informed consent. They were aged of (mean ± SD) 41.2±10.7 years and 80% were of male gender.

SOMAscan proteomic assay, data processing and statistical analysis

Total of 1305 analytes were quantified in patient serum using the SOMAscan high throughput proteomic assay (SomaLogic, Boulder, Colorado, United States of America) at National Jewish Health (Denver, Colorado, United States of America) [S13].

The raw SOMAscan data was standardized by four steps: hybridization normalization, place scaling, median signal normalization and calibration according to manufacturer's instructions (details can be found in SomaLogic's technical notes

(http://somalogic.com/wp-content/uploads/2017/06/SSM-071-Rev-0-Technical-Note-SOMAscan-Data-Standardization.pdf). The standardized expression values were then log2 transformed for downstream analysis. Unsupervised clustering was performed in R, including hierarchical clustering using Pearson correlation as distance measures, and K means clustering with K=2. Functional enrichment was performed with pathway databases including KEGG Reactome and Gene Ontology (GO) pathway database. Differential expression analysis between the two clusters were performed using Limma package [S14]. Proteins with Fold change >1.5 and False discovery rate (FDR)<0.05 was defined as significant. Functional analysis of the differentially expressed proteins were performed based on GO (Biological processes). Additional statistical analysis and plots, including volcano plots and heatmaps, were generated using R, or GraphPad Prism 8.

For two group comparisons, *t* test was performed for data with normal distribution, and Wilcoxon Rank Sum, or Friedman Rank tests was used when normal distribution could not be assumed. Pearson correlation was applied for data with normal distribution and Spearman correlation when normal distribution could not be assumed. ANOVA was used for multi-group comparisons. Fisher exact test and Friedman Rank test were performed for binary data.

Bioinformatical approaches

The bioinformatical approaches are described in Fig 1 in the main manuscript and can be decomposed into three steps:

1. SOMAscan analysis at inclusion: (*i*) hierarchical clustering and identification of contrasted clusters; (*ii*) identification of differentially expressed proteins; (*iii*) GO pathway analysis; *iv*) calculation of a protein score (median expression of identified proteins); (*v*) correlation with clinical parameters; (*vi*) validation of the protein score in an external COPD cohort and in healthy subjects;

2. Identification of short protein signatures associated with each cluster. After exclusion of redundant kinases, phosphatases and adaptor proteins eleven Cluster-2 associated biomarkers were selected by sorting the 10% of the top differentially expressed proteins representative of highly enriched biological processes selected from GO pathway analysis (Tables 1 and S4) performed at visit 1, and exhibited the highest odd-ratios within their corresponding pathways. Cluster-1 associated biomarkers included top four of the 6 up-regulated biomarkers after exclusion of C3b that failed to show any differential expression in the MLCC cohort;

3. follow-up analysis at the second visit: (*i*) hierarchical clustering and identification of contrasted clusters; (*ii*) identification of differentially expressed proteins and assessment of overlap with proteins found at inclusion; (*iii*) monitoring of stable and unstable COPD patients that switched their clusters at follow-up visit using the protein signature.

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Supporting information

S1 Table: characteristics of COPD patients of the COBRA cohort

Parameter	n *	All patients (n = 241)	n *	Patients with 1 visit (n=78)	n *	Patients with 2 visits (n = 163)		p value [a]	p value [b]
		Visit 1		Visit 1 only		Visit 1	Visit 2		
Male sex – no. (%)	241	164 (68.1)	78	50 (64.1)	163	114 (69.9)	-	0.37	-
Age (years)	241	63.1 ± 9.8	78	61.6 ± 11.4	163	63.8 ± 8.9	64.5 ± 9.0	0.14	-
Caucasian origin – no. (%)	239	224 (93.7)	76	70 (92.1)	163	154 (94.5)	-	0.49	-
Other origin – no. (%)	239	15 (6.3)	76	6 (7.9)	163	9 (5.5)	-	0.49	-
GOLD stages									
GOLD I – no. (%)	238	54 (22.7)	75	24 (32.0)	159	28 (17.6)	28 (17.6)	**0.03**	0.99
GOLD II – no. (%)	238	87 (36.5)	75	20 (26.6)	159	66 (41.5)	66 (41.5)	**0.03**	0.99
GOLD III – no. (%)	238	53 (22.3)	75	14 (18.7)	159	38 (23.9)	36 (22.7)	**0.03**	0.99
GOLD IV – no. (%)	238	44 (18.5)	75	17 (22.7)	159	27 (17.0)	29 (18.2)	**0.03**	0.99
Smoking history									
Former smoker – no. (%)	241	149 (61.8)	78	41 (52.6)	163	108 (66.3)	108 (66.3)	**0.002**	1.00
Packs per year in former smokers – no.	147	49.1 ± 23.9	39	49.7 ± 22.2	101	49.7 ± 25.1	49.9 ± 25.1	0.99	0.96
Active smokers – no. (%)	241	84 (34.9)	78	30 (38.5)	163	54 (33.1)	54 (33.1)	**0.002**	1.00
Packs per year in active smokers – no.	82	35.8 ± 21.7	28	35.1 ± 20.8	47	36.0 ± 23.8	34.9 ± 21.9	0.89	0.83
Body Mass Index (kg per m^2)	240	26.5 ± 6.1	77	25.7 ± 5.9	163	26.8 ± 6.2	-	0.21	-
Biology									
Blood leukocytes (no. per mm^3)	165	7500 (6500 - 8900)	43	7400 (6400 - 10000)	96	7350 (6500 - 8750)	7100 (6150 - 8150)	0.37	0.34
Blood eosinophils (no. per mm^3)	165	162 (104 - 230)	43	146 (94 - 213)	96	165 (103 - 225)	162 (117 - 244)	0.37	0.67
With blood eosinophils ≥ 300 per mm^3 – no. (%)	165	27 (16.4)	43	4 (9.3)	96	17 (17.7)	12 (12.5)	0.21	0.32
Blood neutrophils (no. per mm^3)	163	4752 (3840 - 5950)	42	4479 (3782 - 6486)	95	4680 (3835 - 5950)	4560 (3843 - 5265)	0.74	0.39
Blood lymphocytes (no. per mm^3)	165	1830 (1406 - 2280)	43	1920 (1539 - 2438)	96	1648 (1302 - 2190)	1782 (1387 - 2184)	**0.04**	0.49
Blood monocytes (no. per mm^3)	161	560 (444 - 720)	40	603 (469 - 740)	96	532 (404 - 698)	555 (463 - 667)	**0.03**	0.25
Hemoglobin – g per deciliter	115	14.4 ± 1.4	32	14.1 ± 1.6	72	14.6 ± 1.3	14.3 ± 1.4	0.10	0.25
CRP – mg per Liter	112	7.6 ± 7.6	22	6.5 ± 4.6	73	7.8 ± 8.1	6.8 ± 7.5	0.35	0.47
With CRP ≥ 3 mg per Liter – no. (%)	112	85 (75.9)	22	17 (77.3)	73	54 (74.0)	54 (74.0)	0.76	1.00
Blood gases									
PaO_2 - mmHg	181	74.5 ± 14.1	57	74.8 ± 14.2	91	72.9 ± 13.7	74.7 ± 13.2	0.42	0.37
$PaCO_2$ - mmHg	182	39.6 ± 4.8	57	40.0 ± 4.8	90	39.8 ± 4.9	40.0 ± 6.0	0.86	0.86
pH	182	7.42 ± 0.03	57	7.41 ± 0.03	92	7.41 ± 0.03	7.41 ± 0.04	0.78	0.70

S1 Table (continued)

Respiratory function									
Pre-bronchodilator FEV_1 (% predicted)	233	59.6 ± 24.3	72	63.0 ± 27.7	144	56.6 ± 21.7	56.1 ± 21.7	0.10	0.84
Post-bronchodilator FEV_1 (% predicted)	171	63.7 ± 25.8	53	71.3 ± 30.4	70	56.6 ± 22.8	56.5 ± 21.5	**0.005**	0.98
With fixed airflow obstruction – no. (%) [c]	176	143 (81.3)	55	34 (61.8)	70	65 (92.9)	65 (92.9)	**< 0.0001**	1.00
Pre-bronchodilator FVC (% predicted)	233	86.6 ± 21.3	73	86.1 ± 21.9	142	85.0 ± 20.4	84.0 ± 20.4	0.73	0.68
Post-bronchodilator FVC (% predicted)	169	91.5 ± 21.1	51	91.9 ± 21.5	69	91.0 ± 20.4	88.8 ± 21.1	0.83	0.54
Pre-bronchodilator FEV_1 / FVC (% predicted)	235	53.5 ± 15.3	74	57.0 ± 16.7	144	51.4 ± 14.0	51.7 ± 14.2	**0.01**	0.89
Post-bronchodilator FEV_1 / FVC (% predicted)	176	53.9 ± 16.2	55	60.6 ± 17.3	70	47.2 ± 14.4	48.4 ± 14.7	**< 0.0001**	0.62
FRC - %	124	137.8 ± 38.3	49	131.5 ± 31.7	37	140.9 ± 43.4	139.9 ± 41.5	0.27	0.92
RV - %	135	156.4 ± 53.0	53	150.7 ± 43.1	41	165.9 ± 62.9	154.7 ± 56.6	0.19	0.41
TLC - %	137	113.8 ± 19.2	55	112.0 ± 16.9	42	114.1 ± 21.7	112.4 ± 19.5	0.60	0.70
DLCO - %	115	59.0 ± 21.7	46	63.9 ± 21.6	34	49.5 ± 18.8	49.9 ± 18.8	**0.003**	0.94
Symptoms									
With cough – no. (%)	241	97 (40.2)	78	27 (34.6)	163	70 (42.9)	56 (34.4)	0.22	0.12
With wheezing – no. (%)	241	32 (13.3)	78	14 (17.9)	163	18 (11.0)	16 (9.8)	0.14	0.72
With emphysema no. (%) [d]	241	92 (38.2)	78	28 (35.9)	163	64 (39.3)	64 (39.3)	0.62	1.00
With exacerbations in the previous 12 months - no. (%)	241	128 (53.1)	78	39 (50.0)	163	89 (54.6)	62 (38.0)	0.51	**0.003**
Exacerbations in the previous 12 months - no.	241	1.44 ± 0.16	78	1.26 ± 0.22	163	1.52 ± 0.21	1.46 ± 0.23	0.12	0.72
Unscheduled medical visits in the previous 12 months - no.	241	1.19 ± 0.17	78	0.96 ± 0.23	163	1.29 ± 0.22	1.08 ± 0.16	**0.03**	0.09
Hospitalizations for COPD in the previous 12 months – no.	241	0.32 ± 0.05	78	0.41 ± 0.11	163	0.27 ± 0.05	0.19 ± 0.06	0.10	0.17
Comorbidities									
Cardiovascular – no. (%)	241	103 (42.7)	78	32 (41.0)	163	71 (43.6)	-	0.71	-
Hypertension – no. (%)	241	67 (27.8)	78	21 (26.9)	163	46 (28.2)	-	0.84	-
Dyslipidemia – no. (%)	241	58 (24.1)	78	14 (17.9)	163	44 (27.0)	-	0.13	-
Diabetes – no. (%)	241	28 (11.6)	78	7 (9.0)	163	21 (12.9)	-	0.38	-
Sinusitis – no. (%)	241	27 (11.2)	78	7 (9.0)	163	20 (12.3)	-	0.45	-
Allergic rhinitis – no. (%)	241	38 (15.8)	78	12 (15.4)	163	26 (15.9)	-	0.92	-
Obstructive sleep apnea – no. (%)	241	22 (9.1)	78	4 (5.1)	163	18 (11.0)	-	0.14	-
Gastro Esophageal Reflux – no. (%)	241	70 (29.0)	78	21 (26.9)	163	49 (30.1)	-	0.62	-
Bronchial dilatation – no. (%)	241	11 (4.6)	78	3 (3.8)	163	8 (4.9)	-	0.72	-

S1 Table (continued)

Treatments									
On SABA – no. (%)	231	144 (62.3)	70	33 (47.1)	158	110 (69.6)	115 (72.8)	**0.002**	0.54
On LABA alone – no. (%)	233	26 (11.2)	70	5 (7.1)	160	21 (13.1)	18 (11.2)	0.19	0.61
On LAMA alone – no. (%)	233	16 (6.9)	70	4 (5.7)	160	12 (7.5)	12 (7.5)	0.63	1.00
On ICS alone – no. (%)	233	4 (1.7)	70	1 (1.4)	160	3 (1.9)	3 (1.9)	0.82	1.00
Daily dose of ICS - µg of equivalents beclomethasone	119	1304 ± 669	28	1499 ± 811	77	1253 ± 633	1242 ± 626	0.11	0.92
On OCS – no. (%)	232	8 (3.4)	69	7 (10.1)	160	1 (0.6)	2 (1.2)	**0.0003**	0.57
Daily dose of prednisone (mg)	8	20.4 ± 10.9	7	22.6 ± 9.6	1	5	5	0.14	-
On LABA + LAMA – no. (%)	233	22 (9.4)	70	6 (8.6)	160	16 (10.0)	21 (13.1)	0.74	0.39
On LABA + LAMA + ICS – no. (%)	233	78 (33.5)	70	22 (31.4)	160	55 (34.4)	63 (39.4)	0.67	0.36
On anti-histamine – no. (%)	241	20 (8.3)	78	8 (10.3)	162	12 (7.4)	8 (4.9)	0.46	0.36
On theophylline – no. (%)	232	1 (0.4)	69	0 (0.0)	160	1 (0.6)	1 (0.6)	0.52	1.00
On gastro esophageal reflux inhibitors – no. (%)	241	56 (23.2)	78	17 (21.8)	163	39 (23.9)	29 (17.8)	0.72	0.18
On anti-hypertensive drugs – no. (%)	232	80 (34.5)	70	24 (34.3)	160	55 (34.4)	54 (33.7)	0.99	0.91
On statins – no. (%)	231	56 (24.2)	69	11 (15.9)	160	44 (27.5)	49 (30.6)	0.07	0.54
On fibrates – no. (%)	229	5 (2.2)	69	1 (1.4)	157	4 (2.5)	3 (1.9)	0.61	0.71
On anti-platelet aggregation – no. (%)	231	63 (27.3)	69	15 (21.7)	159	47 (29.6)	42 (26.4)	0.23	0.54
Other – no. (%)	227	102 (44.9)	68	20 (29.4)	157	81 (51.6)	75 (47.8)	**0.003**	0.50
On oxygen therapy – no. (%)	238	37 (15.5)	75	11 (14.7)	161	26 (16.1)	16 (9.9)	0.78	0.10
Adherence to treatments – no. (%)	224	203 (90.6)	64	55 (85.9)	155	144 (92.9)	143 (92.3)	0.11	0.83

Data are n (%), or means ± SD, or median (25-75 IQR), or means ± SEM, in case of number of exacerbations, of unscheduled hospital visits and hospitalizations for COPD in the previous 6 months

CRP = C reactive protein; FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; FRC = Functional Residual Capacity; RV = Residual Volume; TLC = Total Lung Capacity; DLCO = transfer factor of the lung for carbon monoxide; ICS = inhaled corticosteroids; SABA = short-acting β2-agonists; LABA = long-acting β2-agonists; OCS = oral corticosteroids; LAMA = long-lasting muscarinic antagonists.

* denotes the number of patients with each available variable

[a] $p \leq 0.05$, between COPD patients with 1 and 2 visits (n=78 and n=163, respectively) (Students' t test, or Mann-Whitney U-test, or Fisher exact test, 2-tailed, or Poisson test).

[b] $p \leq 0.05$, between visits 1 and 2 for n=163 COPD patients (Students' t test, or Mann-Whitney U-test, or Fisher exact test, 2-tailed, or Poisson test).

Supporting information

S2 Table: characteristics of COPD patients of the MLCC cohort

Parameter	n *	All patients, n = 47
Male sex – no. (%)	47	29 (61.7)
Age (years)	47	72.5 ± 9.6
Caucasian origin – no. (%)	47	47 (100)
Other origin – no. (%)	47	0
GOLD stages		
GOLD 1 – no. (%)	47	2 (4.3)
GOLD 2 – no. (%)	47	16 (34.0)
GOLD 3 – no. (%)	47	19 (40.4)
GOLD 4 – no. (%)	47	10 (21.3)
Smoking history		
Never smokers – no. (%)	47	0
Former smoker – no. (%)	47	41 (87.2)
Packs per year in former smokers – no.	47	56.9 ± 32.6
Active smokers – no. (%)	47	6 (12.8)
Packs per year in active smokers – no.	47	89.2 ± 52.1
Body Mass Index (kg per m^2)	31	25.2 ± 6.0
Biology		
Blood leukocytes (no. per mm^3)	45	7800 (6500-9800)
Blood eosinophils (no. per mm^3)	45	200 (100-300)
With blood eosinophils ≥ 300 per mm^3 – no. (%)	45	14 (31.1)
Blood neutrophils (no. per mm^3)	45	5300 (4300-6400)
Blood lymphocytes (no. per mm^3)	45	1600 (1100-2000)
Blood monocytes (no. per mm^3)	45	700 (600-800)
Hemoglobin – g per deciliter	45	13.1 ± 1.6
CRP – mg per Liter	34	1.4 ± 2.9
With CRP ≥ 3 mg per Liter – no. (%)	34	2 (5.9)
Blood gases		
PaO_2 - mmHg	9	66.1 ± 5.4
$PaCO_2$ - mmHg	9	40.5 ± 4.6
Respiratory function		
Pre-bronchodilator FEV_1 (% predicted)	28	39.1 ± 10.5
Post-bronchodilator FEV_1 (% predicted)	29	41.9 ± 14.2
Pre-bronchodilator FVC (% predicted)	28	87.1 ± 16.9
Post-bronchodilator FVC (% predicted)	30	93.1 ± 18.0
Pre-bronchodilator FEV_1 / FVC (% predicted)	28	35.5 ± 9.0
Post-bronchodilator FEV_1 / FVC (% predicted)	29	35.5 ± 10.0
With fixed airflow obstruction – no. (%) [a]	29	28 (96.6)
DLCO (%)	25	41.4 ± 12.4
Symptoms		
With cough – no (%)	46	38 (82.6)
With wheezing – no (%)	47	7 (14.9)
With emphysema no. (%)	25	24 (96.0)
Exacerbations in 12 months - no. (%) [b]	47	1.6 ± 0.7
Hospitalizations for COPD in 12 months - no. [b]	17	0.7 ± 0.7

S2 Table (continued)

Comorbidities		
Cardiovascular – no. (%)	47	22 (46.8)
Diabetes – no. (%)	47	9 (19.1)
Obstructive sleep apnea – no. (%)	47	1 (2.1)
Treatments		
On SABA – no. (%)	47	44 (93.6)
On LABA – no. (%)	43	42 (97.7)
On LAMA – no. (%)	47	25 (53.0)
On ICS – no. (%)	47	43 (91.5)
Daily dose of equivalents beclomethasone	40	842 ± 366
On OCS – no. (%)	47	4 (8.5)
Daily dose of prednisone (mg)	4	4.9 ± 2.3
On oxygen therapy – no. (%)	47	27 (57.4)
Adherence to treatment – no. (%)	12	8 (66.7)

CRP = C reactive protein; FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; DLCO = transfer factor of the lung for carbon monoxide; SABA = short-acting β2-agonists; LABA = long-acting β2-agonists; LAMA = long-lasting muscarinic antagonists; ICS = inhaled corticosteroids = OCS, oral corticosteroids.

Data are n (%), or means ± SD, or median (25-75 IQR), or means ± SEM, for the number of exacerbations

* denotes the number of patients with each available variable

[b] Estimated frequency of exacerbations and hospitalizations based on the events during the study period

S3 Table. Changes in the serum levels of the significantly-regulated proteins between COPD patients from Cluster 1 and Cluster 2

Protein ID	Fold changes	p value *	References
Up-regulated in Cluster 2 versus Cluster 1			
Tropomyosin 4	3.093	8.13E-29	S1-S3
Carbonic anhydrase XIII	3.005	1.73E-29	S4,S5
BTK	2.824	3.08E-33	S6,S7
Cyclophilin F	2.694	7.51E-29	S8
CSK	2.549	3.06E-36	S9-S11
FER	2.537	1.26E-28	S12,S13
PKC-B-II	2.535	1.19E-42	S14
SP-D	2.532	2.39E-24	S15
VAV	2.439	5.27E-27	S16-S18
Histone H1.2	2.420	9.64E-20	S19-S22
GRB2 adapter protein	2.417	1.97E-26	S23,S24
H2A3	2.344	2.10E-19	S19,S22,S25
IMB1	2.316	6.15E-27	S26
DRG-1	2.284	1.16E-32	S27-S29
SRCN1	2.264	9.30E-21	S30,S31
LYN	2.242	1.72E-29	S32,S33
SMAD2	2.206	3.20E-33	S34, S39, S124, S137
NSF1C	2.196	1.83E-26	S35
LYNB	2.182	4.98E-25	S32,S33
NDP kinase B	2.157	6.04E-29	S36-S38
Caspase-3	2.157	3.50E-34	S39
SBDS	2.112	1.97E-30	S40-S42
PDPK1	2.106	4.36E-31	S43,S44
CK2-A1:B	2.097	2.88E-27	S45,S46
RAC1	2.077	3.08E-33	S47-S50
IF4G2	2.064	5.73E-27	S51,S52
eIF-4H	2.051	1.54E-25	S53
Aflatoxin B1 aldehyde reductase	2.045	6.17E-23	S54
Sphingosine kinase 1	2.045	1.28E-27	S55
GAPDH, liver	2.042	8.88E-18	S56,S57
UBE2N	2.034	4.11E-24	S58,S61
α-synuclein	2.011	8.92E-19	S62-S63
SGTA	2.006	3.64E-20	S64
SNAA	1.991	3.45E-23	S65-S68
Haemoglobin	1.966	1.81E-08	S69, S70
METAP1	1.958	3.20E-33	S71,S72
IMDH1	1.957	1.70E-17	S73,S74
PRKACA	1.956	2.18E-30	S75
Annexin I	1.921	2.88E-32	S76,S77

S3 Table (continued)

PKC-A	1.921	2.44E-19	S78
RPS6KA3	1.916	1.57E-33	S79,S80
Histone H2A.z	1.914	5.43E-20	S19,S21,S22,S81,S82
hnRNP A2/B1	1.909	1.84E-29	S83-S85
UFM1	1.888	8.39E-23	S58,S86-S88
FYN	1.886	9.28E-13	S89,S90
RAN	1.861	1.85E-14	S91,S92
Myokinase	1.859	4.43E-11	S93,S94
H2B2E	1.841	4.02E-18	S19,S21,S22,S95
41	1.837	6.00E-16	S96,S97
BARK1	1.835	6.95E-28	S98,S99
M2-PK	1.825	4.82E-15	S100
14-3-3 protein zeta/delta	1.785	1.68E-33	S101-S104
PPID	1.781	2.29E-13	S105-S107
6-phosphogluconate dehydrogenase	1.776	7.82E-8	S108
HXK2	1.775	3.32E-13	S109,S110
PTP-1C	1.756	5.02E-20	S111,S112
DUSP3	1.731	2.39E-25	S113,S114
TCTP	1.723	1.83E-27	S115–S117
Triosephosphate isomerase	1.711	1.39E-23	S118,S119
DLRB1	1.681	8.07E-19	S120,S121
SUMO3	1.680	3.88E-26	S58,S122,S123
PA2G4	1.671	3.51E-15	S124,S125
14-3-3 protein β/α	1.669	3.42E-28	S101-S103,S126
PPAC	1.667	1.62E-08	S127,S128
Transketolase	1.660	1.28E-24	S129,S130
UBC9	1.651	2.16E-31	S58,S86,S131
FGF16	1.650	3.70E-18	S132,S133
EDAR	1.610	1.56E-10	S134,S135
SHC1	1.603	2.71E-25	S136,S137
ARGI1	1.601	2.58E-12	S138-S140
GPVI	1.599	3.60E-13	S141,S142
Cyclophilin A	1.592	3.21E-33	S143,S144
BAD	1.587	3.87E-13	S101,S145
ERK-1	1.566	2.59E-28	S146,S147
PLPP	1.560	9.71E-15	S148,S149
CPNE1	1.560	8.80E-18	S150,S151
BPI	1.554	1.79E-06	S152-S154
NCC27	1.552	1.81E-27	S155,S156
MK01	1.548	2.46E-16	S93,S94
eIF-5A-1	1.544	2.47E-16	S157-S160
NACA	1.539	5.58E-09	S161,S162
AREG	1.538	1.51E-13	S163-S165

S3 Table (continued)

ATPO	1.536	1.71E-13	S166
CD40 ligand	1.524	2.49E-11	S167-S169
Prostatic binding protein	1.519	1.51E-13	S98,S170-S172
Ubiquitin+1	1.512	3.62E-11	S58
Lactoferrin	1.510	9.58E-09	S173
Azurocidin	1.507	5.01E-10	S174,S175
Sorting nexin 4	1.502	1.39E-13	S176
STAT3	1.502	2.02E-26	S46, S50
Up-regulated in Cluster 1 versus Cluster 2			
Glucagon	0.666	1.36E-07	S177
MMP-12	0.652	2.55E-09	S178,S179
Renin	0.650	6.58E-06	S180
Lactadherin (MFGM)	0.640	8.42E-14	S181-S183
C3b	0.637	3.26E-05	S184
Midkine	0.505	1.63E-17	S185-S187

* False discover rate from group comparisons

Abbreviations are listed in the Table 1 of the main manuscript

Bold indicates the 15 proteins belonging to the short signature

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Supporting information

S4 Table: Significant correlations between differentially regulated proteins and the incidence of exacerbations and emphysema in patients with COPD at visit 1.

Biological Hallmarks	Target	Exacerbations (Y/N)		Emphysema (Y/N)	
		OR (2.5-97.5%)	FDR	OR (2.5-97.5%)	FDR
Cell fate, Remodeling and Repair	PRKCA [a]	0.57 (0.41-0.79)	0.016	-	-
	PRKACA [a]	-	-	0.62 (0.41-0.90)	0.0200
	SHC1	-	-	0.33 (0.17-0.58)	0.0026
	eIF-5A-1	-	-	0.43 (0.18-0.60)	0.0026
	TCTP	0.57 (0.36-0.87)	0.0476	0.35 (0.20-0.58)	0.0026
	PA2G4	-	-	0.40 (0.24-0.64)	0.0026
	14-3-3 protein β/α [a]	0.50 (0.30-0.79)	0.0281	0.41 (0.24-0.68)	0.0032
	14-3-3 protein ζ/δ [a]	0.45 (0.28-0.70)	0.0160	0.42 (0.26-0.68)	0.0031
	BAD [a]	-	-	0.45 (0.27-0.70)	0.0031
	RPS6KA3 [a]	0.61 (0.40-0.89)	0.048	0.46 (0.29-0.71)	0.0031
	AREG	-	-	0.46 (0.27-0.75)	0.0065
	METAP1 [a]	-	-	0.50 (0.32-0.76)	0.0044
	FGF16	-	-	0.52 (0.31-0.81)	0.0115
	RAC1 [a]	0.58 (0.40-0.82)	0.022	0.52 (0.35-0.76)	0.0033
	SBDS	0.66 (0.48-0.92)	0.048	0.53 (0.36-0.76)	0.0031
	hnRNP A2/B1	-	-	0.53 (0.36-0.79)	0.0060
	NSF1C	-	-	0.55 (0.39-0.77)	0.0031
	PKC-A [a]	-	-	0.55 (0.38-0.78)	0.0042
	SMAD2 [a]	0.67 (0.49-0.92)	0.048	0.58 (0.40-0.81)	0.0059
	eIF-4H	0.63 (0.45-0.86)	0.028	0.59 (0.41-0.82)	0.0061
	DRG-1	-	-	0.51 (0.35-0.72)	0.0026
	DLRB1	-	-	0.61 (0.39-0.91)	0.025
	PLPP	-	-	0.36 (0.20-0.62)	0.0026
	ARGI1	0.62 (0.43-0.88)	0.047	-	-
	IMB1 [a]	-	-	0.60 (0.43-0.80)	0.003
	ARGI1 [a]	0.62 (0.43-0.88)	0.047	-	-
	41	-	-	0.62 (0.44-0.86)	0.010
	GRB2 adapter protein	0.72 (0.55-0.93)	0.017	0.64 (0.49-0.85)	0.004
	Tropomyosin 4	0.78 (0.64-0.96)	0.024	0.71 (0.57-0.89)	0.004
	Sphingosine kinase 1	0.66 (0.47-0.91)	0.048	0.60 (0.41-0.85)	0.008
	Hemoglobin	-	-	0.72 (0.54-0.93)	0.027
	CSK	-	-	0.64 (0.47-0.86)	0.006
	FYN [a]	-	-	0.74 (0.56-0.97)	0.042
	ERK-1 [a]	0.50 (0.29-0.84)	0.0476	0.41 (0.22-0.72)	0.0062
	MK01/ERK-2	-	-	0.45 (0.26-0.74)	0.0061
	PKC-B-II	0.59 (0.43-0.80)	0.0158	0.55 (0.40-0.76)	0.0026
	Prostatic binding protein	-	-	0.41 (0.24-0.68)	0.0032
	Caspase-3	0.66 (0.47-0.91)	0.048	0.52 (0.35-0.74)	0.0030
	PDPK1 [a]	-	-	0.61 (0.43-0.87)	0.011
	LYN [a]	0.65 (0.47-0.87)	0.029	0.65 (0.47-0.89)	0.013
	LYNB [a]	0.65 (0.48-0.87)	0.028	0.68 (0.50-0.91)	0.016
	CK2-A1:B	-	-	0.56 (0.40-8.80)	0.0164
	NDP kinase B [a]	-	-	0.52 (0.36-0.74)	0.0026
	FER [a]	0.71 (0.55-0.91)	0.016	0.67 (0.51-0.87)	0.004
	RAN [a]	-	-	0.60 (0.42-0.82)	0.0063

S4 Table (continued)

Metabolism and Mitochondria	RAC1	0.58 (0.40-0.82)	0.022	0.52 (0.35-0.76)	0.0033
	α-Synuclein [a]	-	-	0.53 (0.36-0.75)	0.0031
	Cyclophilin F	0.72 (0.57-0.91)	0.016	0.63 (0.50-0.84)	0.003
	Cyclophilin A [a]	0.42 (0.24-0.73)	0.0222	0.31 (0.16-0.57)	0.0026
	SUMO3	-	-	0.38 (0.21-0.63)	0.0026
	UFM1	-	-	0.48 (0.31-0.70)	0.0026
	SNAA	-	-	0.47 (0.31-0.69)	0.0026
	VAV [a]	0.70 (0.53-0.90)	0.040	0.66 (0.49-0.86)	0.006
	14-3-3 protein β/α [a]	0.50 (0.30-0.79)	0.0281	0.41 (0.24-0.68)	0.0032
	14-3-3 protein ζ/δ [a]	0.45 (0.28-0.70)	0.0160	0.42 (0.26-0.68)	0.0031
	BAD	-	-	0.45 (0.27-0.70)	0.0031
	Triosephosphate isomerase	-	-	0.37 (0.21-0.61)	0.0026
	RPS6KA3	0.61 (0.40-0.89)	0.048	0.46 (0.29-0.71)	0.0031
	METAP1	-	-	0.50 (0.32-0.76)	0.0044
	Ubiquitin+1 [a]	-	-	0.37 (0.10-0.66)	0.0045
	UBC9	-	-	0.38 (0.21-0.67)	0.0026
	UBE2N [a]	-	-	0.46 (0.31-0.68)	0.0026
	Carbonic anhydrase XIII	0.80 (0.65-0.99)	0.038	0.74 (0.59-0.94)	0.011
	SRCN1	0.64 (0.49-0.83)	0.016	0.75 (0.57-0.97)	0.035
	M2-PK	0.55 (0.39-0.77)	0.016	0.72 (0.53-0.98)	0.045
	PPAC	-	-	0.64 (0.47-0.85)	0.006
	Transketolase	-	-	0.38 (0.22-0.63)	0.0026
	Aflatoxin B1 aldehyde reductase	-	-	0.61 (0.43-0.84)	0.007
	NCC27	-	-	0.46 (0.25-0.80)	0.0129
	PPID	0.60 (0.43-0.81)	0.016	0.70 (0.51-0.95)	0.033
	Myokinase	-	-	0.64 (0.48-0.85)	0.006
	NACA	-	-	0.53 (0.35-0.79)	0.0061
	SGTA	-	-	0.64 (0.46-0.88)	0.013
	H2A3	0.87 (0.69-1.09)	0.2495	0.81 (0.63-1.04)	0.014
	BTK [a]	0.72 (0.57-0.92)	0.016	0.63 (0.49-0.82)	0.003
	RPS6KA3	0.61 (0.40-0.89)	0.048	0.46 (0.29-0.71)	0.0031
	DUS3	-	-	0.50 (0.30-0.78)	0.0072
	RAC1 [a]	0.58 (0.40-0.82)	0.022	0.52 (0.35-0.76)	0.0033
	CD40 ligand	-	-	0.54 (0.35-0.81)	0.0074
	CPNE1 [a]	0.56 (0.35-0.88)	0.048	0.51 (0.30-0.83)	0.0142
	IMB1	-	-	0.60 (0.43-0.80)	0.003
	PTP-1C	-	-	0.63 (042-0.91)	0.023
	SRCN1	0.64 (0.49-0.83)	0.016	0.75 (0.57-0.97)	0.035
	Annexin I	-	-	0.59 (0.39-0.88)	0.0164
	BARK1	-	-	0.62 (0.41-0.92)	0.026
	GAPDH	0.64 (0.47-0.84)	0.022	0.59 (0.44-0.78)	0.003
	SP-D	-	-	0.76 (0.59-0.97)	0.034
	STAT3	0.47 (0.26-0.83)	0.0476	0.38 (0.20-0.71)	0.0026
	6-Phosphogluconate dehydrogenase	0.68 (0.53-0.85)	0.016	-	-
	ARGI1	0.62 (0.43-0.88)	0.047	-	-
	Midkine	-	-	1.5 (1.1-2.0)	0.014
	Lactadherin (MFGM)	-	-	1.9 (1.3-2.9)	0.006
Tissue injury	**MMP-12**	-	-	1.51 (1.07-2.15)	0.027
	Renin	-	-	1.88 (1.26-2.87)	0.006

[a] These proteins have multiples biological functions and, therefore, they belong to more than one biological process

Bold indicates the 15 proteins belonging to the short signature

Supporting information

S5 Table. Differences in clinical characteristics COPD patients from the MLCC cohort between Cluster 1 and Cluster 2 at inclusion

Parameter	**Cluster 1** (n=34)	**Cluster 2** (n=13)	**p value** *
Male sex – no. (%)	19 (55.9)	10 (76.9)	0.32
Age (years)	73.4 ± 9.3	70.4 ± 10.4	0.35
Caucasian origin – no. (%)	34 (100)	13 (100)	-
Other origin – no. (%)	0	0	-
GOLD stages			
GOLD 1 – no. (%)	2 (5.9)	0 (0.0)	0.80
GOLD 2 – no. (%)	12 (35.3)	4 (30.8)	0.80
GOLD 3 – no. (%)	13 (38.2)	6 (46.2)	0.80
GOLD 4 – no. (%)	7 (20.6)	3 (23.1)	0.80
Smoking history			
Never smokers – no. (%)	0	0	-
Former smoker – no. (%)	32 (94.1)	9 (69.2)	0.07
Packs per year in former smokers – no.	59.5 ± 35.0	47.7 ± 21.0	0.34
Active smokers – no. (%)	2 (5.9)	4 (30.8)	0.07
Packs per year in active smokers – no.	132.5 ± 10.6	67.5 ± 51.1	0.17
Body Mass Index (kg per m^2)	25.7 ± 5.1	23.4 ± 5.6)	0.30
Biology			
Blood leukocytes (no. per mm^3)	7700 (6400-9500)	8200 (7375-9800)	0.40
Blood eosinophils (no. per mm^3)	200 (100-300)	100 (75-200)	0.14
With blood eosinophils ≥ 300 per mm^3 – no. (%)	12 (36.4)	2 (6.7)	0.37
Blood neutrophils (no. per mm^3)	5000 (4100-6400)	5350 (4975- 6350)	0.29
Blood lymphocytes (no. per mm^3)	1500 (1100-2200)	1650 (1475-1925)	0.55
Blood monocytes (no. per mm^3)	700 (500-800)	700 (675-1000)	0.24
Hemoglobin – g per deciliter	12.9 (1.7)	13.5 (1.5)	0.32
CRP – mg per Liter	1.5 (3.4)	1.1 (1.0)	0.73
With CRP ≥ 3 mg per Liter – no. (%)	2 (8.3)	0 (0.0)	0.89
Respiratory function			
Pre-bronchodilator FEV_1 (% predicted)	44.6 (15.8)	33.0 (12.0)	0.11
Post-bronchodilator FEV_1 (% predicted)	45.9 (16.4)	35.5 (12.6)	0.17
Pre-bronchodilator FVC (% predicted)	90.5 (16.2)	84.5 (24.8)	0.49
Post-bronchodilator FVC (% predicted)	95.3 (20.5)	87.7 (22.1)	0.44
Pre-bronchodilator FEV_1 / FVC (% predicted)	38.2 (9.9)	30.0 (4.4)	0.06
Post-bronchodilator FEV_1 / FVC (% predicted)	37.8 (10.2)	30.8 (5.0)	0.13
DLCO (%)	47.3 (13.6)	37.2 (5.9)	0.13

S5 Table (continued)

Symptoms			
With cough – no (%)	28 (82.4)	10 (83.3)	1.00
With wheezing – no (%)	3 (8.8)	4 (30.8)	0.15
With emphysema no. (%)	30 (88.9)	5 (38.5)	**0.001**
Comorbidities			
Cardiovascular – no. (%)	18 (52.9)	4 (30.8)	0.20
Diabetes – no. (%)	8 (23.5)	1 (7.7)	0.11
Treatments			
On SABA – no. (%)	32 (94.1)	12 (92.3)	1.00
On LABA – no. (%)	32 (94.1)	9 (69.3)	**0.04**
On LAMA – no. (%)	32 (100.0)	10 (90.9)	0.57
On ICS – no. (%)	32 (94.1)	11 (84.6)	0.65
Daily dose of equivalents beclomethasone	864.1 ± 382.3	752.5 ± 298.2	0.45
On oxygen therapy – no. (%)	21 (61.8)	6 (46.2)	0.52

Data are n (%), or means ± SD, or median (25-75 interquartile range), or means ± SEM, for the number of exacerbations

CRP = C reactive protein; FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; DLCO = transfer factor of the lung for carbon monoxide; SABA = short-acting β2-agonists; LABA = long-acting β2-agonists; LAMA = long-lasting muscarinic antagonists; ICS = inhaled corticosteroids.

* Students' t test, or Fisher exact test 2-tailed, or Mann-Whitney U-test

[a] Estimated frequency of exacerbations and hospitalizations, according to the events during the study period

Supporting information

S6 Table. Main clinical characteristics of COPD patients switching of Clusters between visit 1 and visit 2

Parameter	Values at visit 1	Values at visit 2	p value *
COPD patients switching from Cluster 1 at visit 1 to Cluster 2 at visit 2 (n = 29)			
With emphysema - no. (%) [b]	16 (55.2)	13 (44.8)	0.44
DLCO - %	49.4 ± 13.3	54.3 ± 28.5	0.60
With exacerbations in the previous 12 months - no. (%)	20 (69.0)	11 (37.9)	**0.02**
With unscheduled medical visits in the previous 12 months - no. (%)	16 (55.2)	8 (27.6)	**0.04**
With hospitalizations for COPD in the previous 12 months – no. (%)	8 (27.6)	1 (3.4)	**0.02**
On SABA – no. (%)	19 (65.5)	18 (69.2)	1.00
On LABA – no. (%)	22 (75.9)	20 (70)	0.77
On LAMA – no. (%)	19 (65.5)	20 (70)	1.00
On ICS – no. (%)	13 (44.8)	15 (51.7)	0.79
On anti-hypertensive drugs – no. (%)	12 (41.4)	10 (38.5)	0.79
On statins – no. (%)	11 (37.9)	10 (38.5)	1.00
Adherence to treatment – no. (%)	26 (89.7)	26 (89.7)	1.00
COPD patients switching from Cluster 2 at visit 1 to Cluster 1 at visit 2 (n = 26)			
With emphysema - no. (%)	5 (19.2)	11 (42.3)	0.08
DLCO - %	53.6 ± 18.0	53.4 ± 10.9	0.99
With exacerbations in the previous 12 months - no. (%)	15 (57.7)	10 (38.5)	0.17
With unscheduled medical visits in the previous 12 months - no. (%)	10 (38.5)	8 (30.8)	0.56
With hospitalizations for COPD in the previous 12 months – no. (%)	1 (4)	6 (23.1)	**0.05**
On SABA – no. (%)	20 (69)	19 (73.1)	1.00
On LABA – no. (%)	18 (62.1)	21 (80.8)	0.52
On LAMA – no. (%)	12 (46.2)	20 (76.9)	**0.04**
On ICS – no. (%)	13 (50)	15 (57.7)	0.74
On anti-hypertensive drugs – no. (%)	7 (24.1)	8 (30.8)	1.00
On statins – no. (%)	2 (6.9)	3 (11.5)	1.00
Adherence to treatments - no. (%)	23 (92.0)	24 (100.0)	1.00

Data are expressed as numbers (%) and as means ± SD

DLCO = transfer factor of the lung for carbon monoxide; SABA = short-acting β2-agonists; LABA = long-acting β2-agonists; LAMA = long-lasting muscarinic antagonists; ICS = inhaled corticosteroids.

* Students' t test or Fisher exact test 2-tailed