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Lung tissue gene expression profile of eosinophilic chronic obstructive pulmonary disease

Lung Research Center Symposium

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Blood eosinophil is a biomarker for COPD

What molecular pathways are altered in the lungs of eosinophilic COPD?

Blood eosinophil counts predicts COPD exacerbations and response to inhaled corticosteroids
It is not known **if eosinophils in the blood reflect eosinophils in the lung**
Or **what pathways are altered in the lung**

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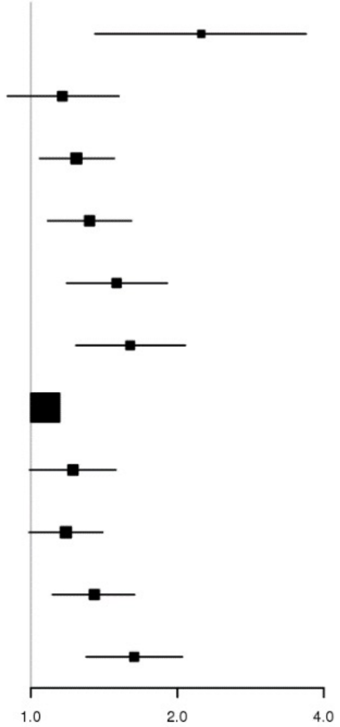
Eosinophil Cutoff	n	n	IRR	95% CI
cell/uL continuous	NA	1540	2.24	1.35-3.68
100 cells/uL	223	1330	1.16	0.90-1.52
200 cells/uL	814	739	1.24	1.04-1.48
300 cells/uL	1187	366	1.32	1.08-1.61
340 cells/uL	1350	203	1.5	1.18-1.91
400 cells/uL	1398	155	1.6	1.24-2.08
% continuous	NA	1540	1.07	1.02-1.11
2 %	408	1145	1.22	0.99-1.50
3 %	859	694	1.18	0.99-1.40
4 %	1166	387	1.35	1.11-1.63
5 %	1334	219	1.63	1.30-2.05



Yun et al. JACI 2018

Gene expression of eosinophilic COPD from lung tissue

1432 lung RNAseq

↓

562 with CBC

↓

31 with fibrosis
114 with systemic steroids
30 with missing variables
4 with eosinophils >1 yr

383 for analysis

↓

Differential Expression

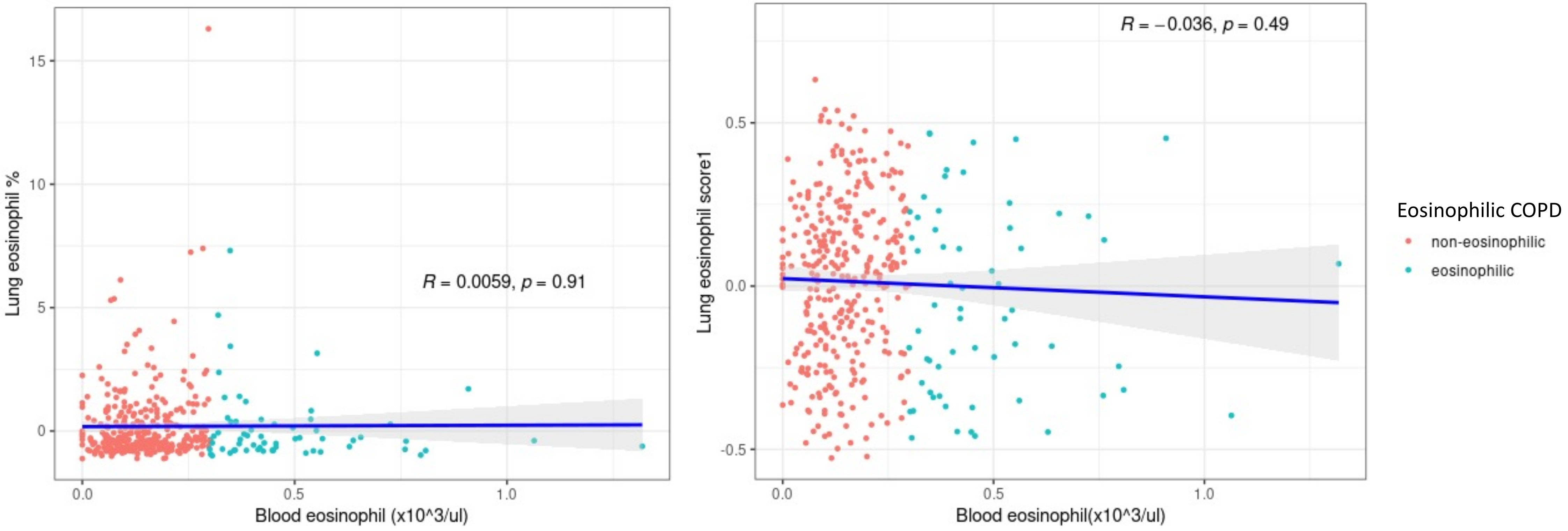
	Non-eosinophilic COPD (n=322)	**Eosinophilic COPD (n=61)**	**P value**
Age (mean ± SD)	65 ± 9	66 ± 10	0.75
Male (%)	172 (53)	41 (67)	0.06
White race (%)	294 (91)	57 (93)	0.43
Current smokers (%)	27 (8)	4 (7)	0.82
Smoking history (PY)	46 ± 32	41 ± 31	0.2
History of asthma (%)	65 (20)	13 (21)	<0.01
ICS (%)	140 (44)	24 (39)	0.65
FEV1% predicted (mean ± SD)	59 ± 26	67 ± 23	0.05
BMI (mean ± SD)	26 ± 5	28 ± 5	<0.01
Emphysema path (%)	260 (80)	45 (74)	0.6
WBC (mean ± SD)(x10^3/ul)	7.8 ± 3	8.5 ± 2	0.07
Eosinophil % (mean ± SD)	2 ± 1	6 ± 3	<0.01

Eosinophilic COPD is associated with metabolic pathways and not enriched for eosinophil genes

Category	Number of genes	Description
Differentially expressed genes	2 (FDR ≤ 0.05)	***CRELD2*** (ER resident chaperone) ***UQCC2*** (mitochondrial complex III component)
Pathways	54 (FDR ≤ 0.15)	Glycolysis pathway

Adjusted for age, sex, self-reported race, current smoking status, pack-years of smoking, inhaled corticosteroid use, library batch

Statistical estimation of eosinophil abundance
No association between blood and lung eosinophils



Statistical deconvolution

Eosinophil gene score

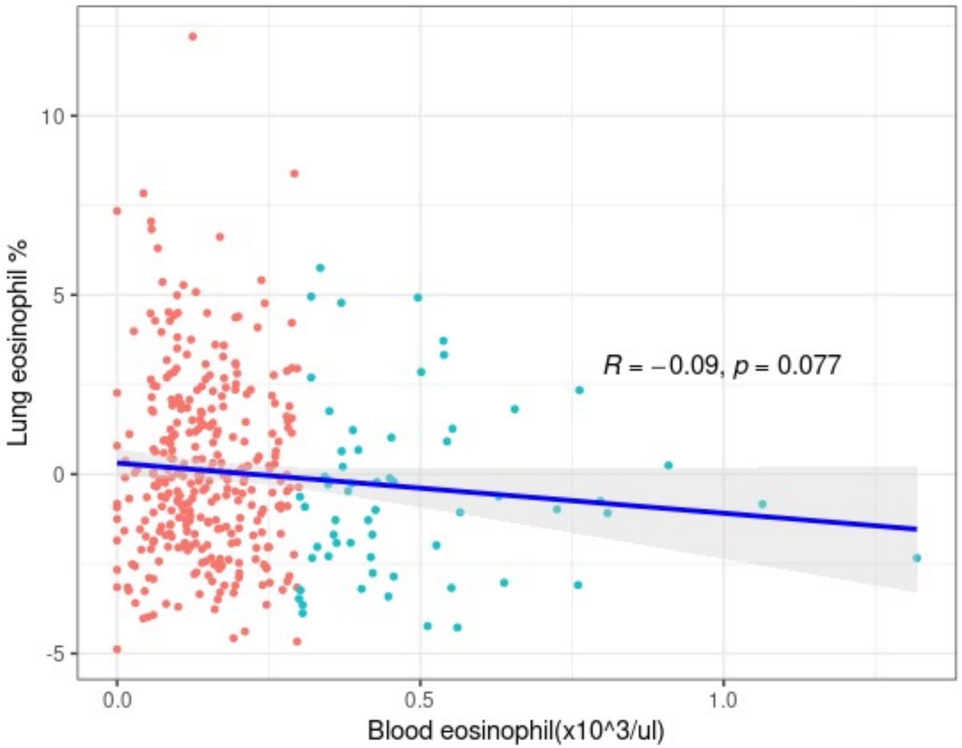
Multivariable linear regression analysis

lung eosinophils are differentially correlated by eosinophilic and non-eosinophilic COPD status

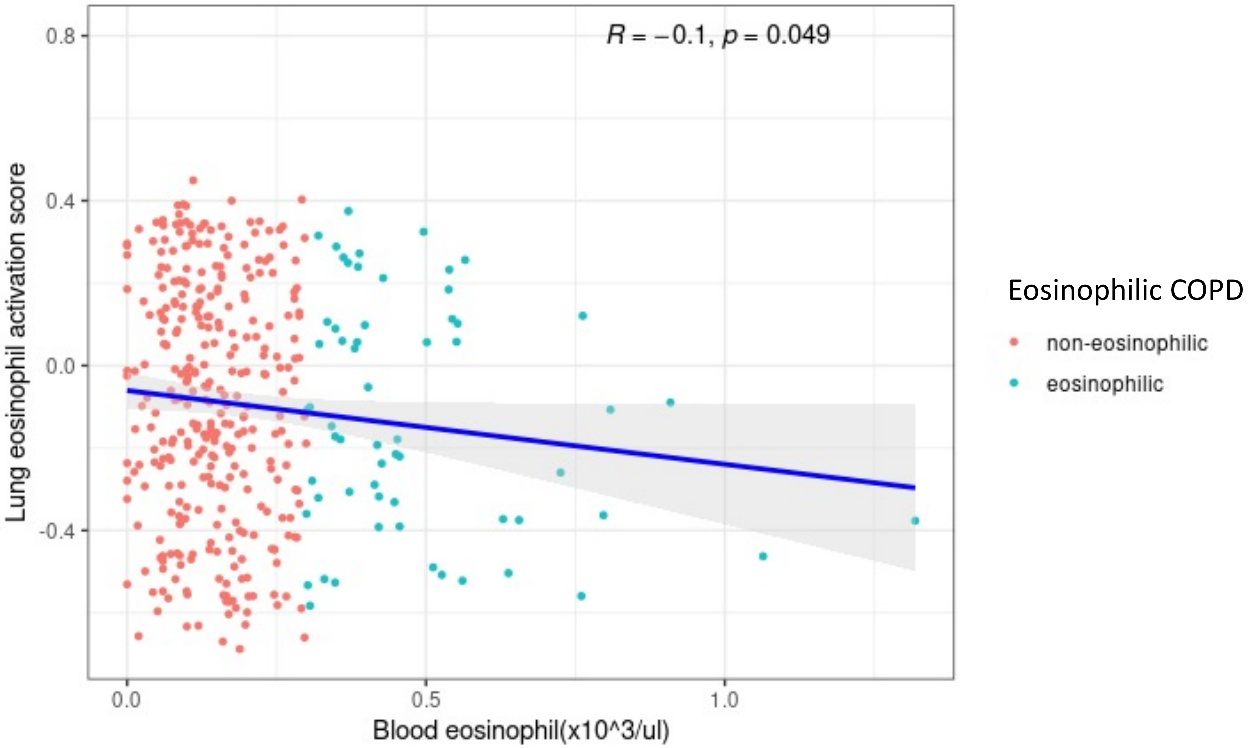
	All subjects (n=383)	**Non-eosinophilic COPD (n=322)**	**Eosinophilic COPD (n=61)**
Blood eosinophil count	-0.03	**0.36** (p <0.05)	0.054
Age	**0.005** (p <0.001)	**0.005** (p <0.01)	0.005
Sex	0.00	0.017	-0.07
Race	0.04	0.04	-0.04
Current smoking	0.04	0.06	-0.05
ICS	0.02	-0.02	**0.23** (p <0.01)

Statistical estimation of activated eosinophils
Negative association between activated eosinophils

Statistical deconvolution



Eosinophil gene score



Johansson. Clin.Exp.Allergy 2014

Multivariable linear regression analysis

Blood and lung activated eosinophils are inversely correlated

	All subjects (n=383)	Non-eosinophilic COPD (n=322)	Eosinophilic COPD (n=61)
Blood eosinophil count	**-0.2** (p <0.05)	-0.25	**-0.34 (p = 0.08)**
Age	0.00	0.00	0.00
Sex	**0.07** (p <0.05)	0.06 (p = 0.09)	0.16
Race	0.1	0.1 (p = 0.09)	0.05
Current smoking	**0.12** (p<0.05)	0.1 (p = 0.08)	0.18
ICS	0.03	0.01	**0.15 (p = 0.06)**

Summary and Future directions

1. Eosinophilic COPD is associated with metabolic pathways in the lung

2. Blood and lung eosinophil counts are correlated in non-eosinophilic subjects.
In subjects with eosinophilic COPD, lung eosinophils and activated eosinophil counts are associated with ICS use suggesting differential response to ICS.

3. We will analyze matched lung histology samples to further characterize the location and the heterogeneity of eosinophils in eosinophilic and non-eosinophilic patients.