Changes in the Gut Microbiome in Chronic Obstructive Pulmonary Disease

S. F. Rehman[1], K. L. Bowerman[2], N. Lachner[3], K. F. Budden[1], R. Kim[4], D. L. Wood[2], S. L. Gellatly[1], P. A. Wark[5], P. Hugenholtz[2], P. M. Hansbro[6]; [1]Priority Research Centre for Healthy Lungs,Hunter Medical Research Center, The University of Newcastle, Newcastle, Australia, [2]Australian Centre for Ecogenomics,School of Chemistry and Molecular Biosciences, The University of Queensland, Queensland, Australia, [3]School of Chemistry and Molecular Biosciences, The University of Queensland, Queensland, Australia, [4]Centre for Inflammation,Centenary Institute, University of Technology Sydney,NSW, Sydney, Australia, [5]Respiratory and Sleep Medicine, John Hunter Hosp, New Lambton NSW 2322, Australia, [6]Priority Research Centre for Healthy Lungs,Hunter Medical Research Center,, Centre of Inflammation.Centenary Institute,The University Technology Sydney &The University of Newcastle, Sydney, Australia.

Corresponding author's email: saimafirdous.rehman@uon.edu.au

RATIONALE: Chronic obstructive pulmonary disease (COPD) is the third commonest cause of death globally. COPD is a heterogeneous inflammatory disease state with no effective treatments that reverse or halt its progression. The lung microbiome is a contributing factor in COPD however the gut microbiome has not been widely examined. We hypothesized that changes in the gut microbiome may be linked to COPD. We compared the gut microbiota in COPD patients with healthy controls using untargeted fecal metagenomics. METHODS: We characterized gut microbiota in stool from individuals satisfying the Global initiative for chronic obstructive lung disease (GOLD) criteria for COPD. Twenty-eight COPD (54% female) and 29 healthy controls (66% female) were recruited. Healthy controls were adults >40 years old with no history of cardiac or respiratory disease and with normal lung function measured by spirometry (FEV1/FVC ratio >0.7 and FEV1 >80% predicted. Statistical comparison of metadata characteristics between COPD and healthy groups was undertaken in R using either Student's t test or Wilcoxon sum test dependent on normality estimation using Shapiro Wilk test.16S rRNA gene sequencing and metagenomics were undertaken to compare the gut bacterial composition between COPD patients and healthy individuals. RESULTS: Using 16S rRNA gene sequencing, 4,285 variants were identified across all 57 samples. This, and metagenomics, showed that 146 species across 107 genera differed in abundance between the groups, with Streptococci key differentiators. COPD and healthy samples could be distinguished ($P<0.001$) despite considerable variation in community composition between individuals and no significant difference in diversity between the groups ($P_{Shannon}=0.329$, $P_{SimpsonInverse}=0.291$). Random forest analysis classified subjects according to COPD status with 77% (kappa=0.53) accuracy. Bifidobacteriaceae, Eubacteriaceae, Lactobacillaceae, Micrococcaceae, Streptococcaceae and Veillonellaceae were enriched at the family level in COPD. Depleted families included Desulfovibrionaceae, Gastranaerophilaceae and Selenomonadaceae along with several uncharacterised families of Bacilli and Clostridia. DESeq2 and MixOmics approaches identified, significantly enriched or depleted genera between

COPD and healthy samples.The abundance of some bacteria were also associated with specific disease characteristics, with the abundance of Blautia_A, Dorea faecis, and Eubacterium_E linked to blood and lung function metrics. CONCLUSION: This study defined altered gut microbiomes associated with disease features in COPD, and identifies new potential biomarkers and therapeutic targets.

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