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COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: informahealthcare.com/journals/icop20

Journal Club

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To cite this article: Ron Balkissoon (2010) Journal Club, COPD: Journal of Chronic Obstructive Pulmonary Disease, 7:4, 310-311, DOI: 10.3109/15412555.2010.500599

To link to this article: https://doi.org/10.3109/15412555.2010.500599

Published online: 30 Jul 2010.

COPD: Journal of Chronic Obstructive Pulmonary Disease, 7:310–311
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2010.500599

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Multidrug Resistance-Associated Protein-1 (MRP1) Genetic Variants, MRP1 Protein Levels and Severity of COPD. S.E. Budulac, D.S. Postma, P.S. Hiemstra, L.I. Kunz, M. Siedlinksi, H.A. Smit, J.M. Vonk, B. Rutgers, W. Timens, H.M. Boezen, Lung Disease Glucold Study Group TG (Respir Res 2010 May 20;11(1):60). [Epub ahead of print]

Background. Multidrug resistance-associated protein-1 (MRP1) protects against oxidative stress and toxic compounds generated by cigarette smoking, which is the main risk factor for chronic obstructive pulmonary disease (COPD). We have previously shown that single nucleotide polymorphisms (SNPs) in MRP1 significantly associate with level of FEV_1 in 2 independent population based cohorts. The aim of our study was to assess the associations of MRP1 SNPs with FEV_1 level, MRP1 protein levels and inflammatory markers in bronchial biopsies and sputum of COPD patients.

Methods. Five SNPs (rs212093, rs4148382, rs504348, rs4781699, rs35621) in MRP1 were genotyped in 110 COPD patients. The effects of MRP1 SNPs were analyzed using linear regression models.

Results. One SNP, rs212093 was significantly associated with a higher FEV1 level and less airway wall inflammation. Another SNP, rs4148382 was significantly associated with a lower FEV_1 level, higher number of inflammatory cells in induced sputum and with a higher MRP_1 protein level in bronchial biopsies.

Conclusions. This is the first study linking MRP1 SNPs with lung function and inflammatory markers in COPD patients, suggesting a role of MRP_1 SNPs in the severity of COPD in addition to their association with MRP1 protein level in bronchial biopsies.

Comments. The study evaluated 5 SNPs for MRP1 and found rs4148382 associated with lower lung function and higher numbers of inflammatory cells in induced sputum and with higher MRP1 protein levels in bronchial biopsies. The study only had 110 patients and needs to be replicated with a larger cohort of COPD patients. Nonetheless it points to the significant role of genetics in determining susceptibility, severity and no doubt the subphenotypes of COPD. It also further supports the significant role of oxidative stress in COPD.

Colour of Sputum is a Marker for Bacterial Colonisation in Chronic Obstructive Pulmonary Disease. M. Miravitlles, A. Marin, E. Monso, S. Vila, C. de la Roza, R. Hervas, C. Esquinas, M. Garcia, L. Millares, J. Morera, A. Torres (Respir Res 2010 May 14;11(1):58). [Epub ahead of print]

Background. Bacterial colonisation in chronic obstructive pulmonary disease (COPD) contributes to airway inflammation and modulates exacerbations. We assessed risk factors for bacterial colonisation in COPD.

Methods. Patients with stable COPD consecutively recruited over 1 year gave consent to provide a sputum sample for microbiologic analysis. Bronchial colonisation by potentially pathogenic microorganisms (PPMs) was defined as the isolation of PPMs at concentrations of [greater than or equal to] 102 colony-forming units (CFU)/mL on quantitative bacterial culture. Colonised patients were divided into high (>105 CFU/mL) or low (<105 CFU/mL) bacterial load.

Results. A total of 119 patients (92.5% men, mean age 68 years, mean forced expiratory volume in one second [FEV1] [% predicted] 46.4%) were evaluated. Bacterial colonisation was demonstrated in 58 (48.7%) patients. Patients with and without bacterial colonisation showed significant differences in smoking history, cough, dyspnoea, COPD exacerbations and hospitalisations in the previous year, and sputum colour. Thirty-six patients (62% of those colonised) had a high bacterial load. More than 80% of the sputum samples with a dark yellow or greenish colour yielded PPMs in culture. In contrast, only 5.9% of white and 44.7% of light yellow sputum samples were positive ($P < 0.001$). Multivariate analysis showed an increased degree of dyspnoea (odds ratio [OR] = 2.63, 95% confidence interval [CI] 1.535.09, $P = 0.004$) and a darker sputum colour (OR = 4.11, 95% CI 2.307.29, $P < 0.001$) as factors associated with the presence of PPMs in sputum.

Conclusions. Almost half of our population of ambulatory moderate to very severe COPD patients were colonised with PPMs. Patients colonised present more severe dyspnoea, and

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a darker colour of sputum allows identification of individuals more likely to be colonised.

Comments. Numerous publications have suggested that sputum color cannot be used to predict presence or absence of potential bacterial pathogens yet this study lends credence to what many clinicians feel is a valid tool to judge potential benefit of antibiotic therapy. It is also interesting to note that about 50% of patients who have exacerbations demonstrate a potential microbial pathogen. Given that not all COPD patients are the same there may be more than one type of exacerbation group, (i.e., those who are chronically colonized and those who are not). Identifying the various subgroups may lead to differences in approaches to maintenance and acute treatment.

Potential Role of Stem Cells in Management of COPD. T.L. Hackett, D.A. Knight, D.D. Sin (Int J Chron Obstruct Pulmon Dis 2010 Apr 7;5:818–818).

Chronic obstructive pulmonary disease (COPD) is a worldwide epidemic affecting over 200 million people and accounting for more than three million deaths annually. The disease is characterized by chronic inflammation of the airways and progressive destruction of lung parenchyma, a process that in most cases is initiated by cigarette smoking. Unfortunately, there are no interventions that have been unequivocally shown to prolong survival in patients with COPD. Regeneration of lung tissue by stem cells from endogenous and exogenous sources is a promising therapeutic strategy. Herein, we review the current literature on the characterization of resident stem and progenitor cell niches within the lung, the contribution of mesenchymal stem cells to lung regeneration, and advances in bioengineering of lung tissue.

Comment. This is an excellent literature review and summary on the current state-of-the-art of stem cell research for COPD. The authors provide a very nice background section on the mechanisms of structural damage, cellular aging and senescence in COPD then discusses various ways stem cell technology my be used to repair damaged lung through either enhancing resident stem cells, bioengineering lung tissue or using mesenchymal stem cells. This is a nice introduction for those unfamiliar with stem cell research as to the potential applications not only for COPD but for other lung diseases.