Reviewer’s report

Title: The rs361525 polymorphism does not increase production of Tumour Necrosis Factor Alpha by monocytes from Alpha-1 Antitrypsin Deficient subjects with Chronic Obstructive Pulmonary Disease

Version: 0 Date: 19 Sep 2015

Reviewer: Caroline Owen

Reviewer's report:

General comments

Gane et al have investigated whether the rs361525 polymorphism in the TNF-alpha promoter regulates the production of TNF-alpha by monocytes from COPD patients with inherited alpha-1-antitrypsin deficiency (AATD). The results show similar production of TNF-alpha by monocytes from subjects with and without the polymorphism both at the steady state mRNA level and the secreted protein level.

Strengths of the manuscript are that there is a sound rationale for conducting the study as: 1) prior studies show that COPD patients with AATD and chronic bronchitis having this SNP have 100-fold more TNF-alpha in their sputum than subjects without this SNP; and 2) TNF-alpha likely contributes to the inflammatory process in the lungs of patients with AATD and COPD. The studies are novel, the methods are sound, and the experiments have been conducted on primary cells from patients that have been carefully phenotyped and well matched. Also, the results are clear cut, and the manuscript is clearly written, and the limitations of the study have been discussed. Overall, this is an important negative finding that should be in the public domain.

Major comments: None

Minor discretionary revision:

1. Among subjects with the TNF-alpha polymorphism, AATD patients having the chronic bronchitis phenotype are the subgroup that have 100-fold higher sputum levels of TNF-alpha. Although it is recognized that AATD is relatively uncommon and only a small number of subjects could be studied, Table 1 shows that ~50% of the AATD patients with the polymorphism have chronic bronchitis. Can the authors run a subgroup analysis to see whether monocytes from the 4 chronic bronchitis patients with the polymorphism have higher (or trends towards higher) TNF-alpha expression or secretion than cells from the 9 AATD patients without the polymorphism or the 5 chronic bronchitis group without the polymorphism?
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An article of importance in its field

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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