Reviewer's report

Title: Induction of autoantibodies against lung matrix proteins and smoke-induced inflammation in mice

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Reviewer: Jeffrey Curtis

Reviewer's report:

General Comments

This study, from a group that has already published significant results in multiple areas of COPD pathogenesis, addresses the important goal of defining whether autoantibody production in COPD is an epiphenomenon or etiologic. They used a novel immunization protocol, and the nose-only method of murine smoke exposure, which, while laborious, has the advantage of minimizing enteral deposition of cigarette-derived substances as occurs in whole mouse exposure methods due to grooming. The study is carefully designed and executed, with an appropriate range of complementary endpoints.

The results are largely negative, in that the principal goal, "to test whether induction of autoantibodies against lung matrix proteins can augment the smoke-induced inflammatory response" was not attained. Stating that the study was negative should not be taken to be a damning comment, as the published literature in the field of murine smoking models is heavily biased toward positive studies, relative to the results presented in abstract form at scientific meetings. Thus, publication by respected groups of less spectacularly conclusive results serves a purpose.

Major Compulsory Revisions

1. The manuscript would benefit from a more definitive statement in the Discussion of what the authors believe their mixed results (e.g., absence of an additive effect of immunization and smoking) mean. Can these results be taken to refute the theory that autoantibodies are causative of emphysema?

2. Possible reasons for the lack of emphysema in response to six months of smoke-exposure should also be discussed. For example, the choice of the C57BL/6 strain, which is a low-responder in most labs; another possibility is that the smoke exposure was really modest compared to many published protocols.

Minor Essential Revisions

Discussion: (2nd paragraph): The sentence "the immunization with lung matrix proteins was most prominent for decorin: is ambiguous. Do the authors mean that the effect, as measured by antibody titer, was greatest for this antigen?
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests