Author's response to reviews

Title: Viruses and chronic pulmonary disease: The role of immune modulation

Authors:

Aran Singanayagam (a.singanayagam@imperial.ac.uk)
Priya V Joshi (priyavjoshi@yahoo.co.uk)
Patrick Mallia (p.mallia@imperial.ac.uk)
Sebastian L Johnston (s.johnston@imperial.ac.uk)

Version: 4  Date: 19 January 2012

Author's response to reviews:

19/01/2012

Dear Editor

I have attached your comments followed by my responses.

1. Title: Viruses exacerbating chronic pulmonary disease: The role of immune modulation. Since your review does not focus on the role of viruses in the inception chronic respiratory diseases, but rather exacerbation these diseases of ref 1 and 2 thought that a change it title would be more appropriate.

   - I am happy with this change but we have provided data regarding the possible role of chronic virus infection in the pathogenesis of COPD. There is very little data about this compared to the amount of data regarding the role of viruses in acute exacerbations and therefore the main focus of the review was bound to be acute exacerbations.

2. Introduction: This is a generally well written and informative introduction, and I have no comments on the style of this. However, Referee 1 notes that one comment regarding the differences and similarities between the diseases you discuss is a little overstated. You discuss later in this article there is more of a connection between COPD and asthma than there is between either of these and CF. Therefore, please add a brief sentence here to clarify this.

   - I have added a sentence here.

3. Induction of chronic respiratory diseases by viruses: Reviewer 2 notes that although not the focus of your article, it would be useful to have a brief discussion here on the known roles of viruses in the induction of chronic respiratory diseases, especially asthma with reference to recent reviews.

   - I have added a section regarding this topic however this is a major (and controversial) topic in its own right and can only be discussed briefly in this review. As there is only really evidence for viruses in asthma induction I wonder
whether it would be better including this section in the 'Asthma' section rather than on its own? Also if this is included would it be better to leave the original title as it was?

4. Mechanisms of virus-induced exacerbations: Reviewer 3 notes that this section focuses more on the importance of understanding mechanisms of virus-induced exacerbations, rather than discussing the relevant literature outlining the current knowledge of how viral infections may result in acute exacerbations (which you go on to do in subsequent sections in any case). Therefore, I have changed the heading of this section to make it clearer to the reader its content. Please check and modify if appropriate.

- OK.

5. Figure 1: Please add a legend and brief title to your figure.

- Figure 1. Consequences of virus infection in healthy individuals and asthmatics. Virus infection in non-asthmatics (left-hand panel) induces robust interferon and Th1 cell responses with rapid control of viral replication and minimal inflammation. In asthmatics impaired interferon and Th1 responses results in uncontrolled viral replication and an exaggerated inflammatory response.

6. Inflammatory and immune responses to virus infection in asthma: Firstly, Referee 2 notes that the IFN-lambda discussion occurs in the middle of the IFN-beta discussion. I have moved this sentence to later in the discussion. Please check to ensure you are happy with this change. Secondly, Referee 1 highlights that one interesting issue is that asthma (and perhaps atopy) may be related to a relative impaired IFN response. It would be very interesting if you could here (see comment 9) briefly discuss any hypotheses on this, expanding on the sentence I have highlighted. Referee 1 notes that you may wish to discuss why is there such compelling evidence for specific respiratory viruses to drive exacerbations. Lastly, in this section, Referee 1 notes that you focus on the epithelium and Th2 cells, but there are many reports showing abnormalities in macrophages and NKT cells that are associated with asthma exacerbations. It may be helpful to add a small section discussing these cells. Please consider doing so.

- There are a large variety of immune cells involved in the inflammatory responses in asthma exacerbations. In the section 'Inflammatory Responses to Virus Infection in Asthma' I have added a section about the cellular inflammatory response and moved the section regarding T cells here and discussed the role of macrophages. I would disagree with the reviewer's reference to NK cells. There was a paper reporting high numbers on invariant NKT cells in asthma but this was subsequently shown to false. The data that is available refers to NK cells in stable asthma (and there is not much data regarding this) and no studies of NK cells in asthma exacerbations.

7. Mechanisms of virus-induced COPD exacerbations: Referee 3 notes that it
would be helpful if the murine COPD model could be discussed in a little greater
detail so that the reader has some idea about how this model was generated and
the way in which it mimics COPD. For instance, is this a model in which the
animals were exposed to cigarette smoke or was this a transgenic model?

- I have added a sentence describing the mouse model.

8. Virus infection and stable COPD: In this section, you discuss a study on RSV
frequency in acute versus stable state. Referee 3 asks if there a control group
without COPD for the study described here. This will help the reader know
whether the detection rate is greater in COPD subjects compared to subjects
without this disease.

- There was no non-COPD group in this study.

9. Suppression of antiviral responses: Referee 2 notes that a discussion of the
potential role of viruses, particularly more virulent strains, in suppressing
anti-viral responses themselves could be incorporated. You have mentioned this
in several places in your manuscript specific to the chronic respiratory disease of
that section. I think it would be useful to have a section summarizing this (for
which I have suggested this subheading), and then expanding upon the potential
role of viruses in this process.

- There exists substantial literature regarding the mechanisms viruses have
developed to evade host immune responses. We have not included this because
most data focuses on viruses that are not involved in exacerbations (apart from
influenza) and because the review is focussed on the host response and how this
may differ in individuals with chronic lung disease. As there is no evidence that
patients with lung disease are more susceptible to viruses that suppress the host
response, discussion of these mechanisms is beyond the scope of this article as
it does not account for why individuals with chronic lung disease develop
exacerbations when infected with relatively non-virulent viruses such as
rhinoviruses.

10. Bacteria-virus interactions in pulmonary disease: In this section, both referee
1 and 2 note that it would be useful to mention some of the studies showing a
potential role for bacteria in exacerbations of asthma.

- If we discuss the role of bacteria in asthma then we should also include their
role in COPD and CF but this is a whole topic in its own right and beyond the
scope of this article that specifically refers to the role of viruses. We feel that
discussion of bacteria is only relevant in how these may interact with viruses
which is why we have limited it to this area only.

11. List of abbreviations: As pointed out by referee 2, there are many
abbreviations here, so it would be useful to have a list here. However, they
should be defined in the text at first use also.

- I have done this
12. Please add the following sections to your manuscript:

Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

- I have done this