Author’s response to reviews

Title: Low CD1c+ myeloid dendritic cell counts correlated with a high risk of rapid disease progression during early HIV-1 infection

Authors:

Yingying Diao (cmudyy@163.com)
Wenqing Geng (windygeng@163.com)
Xuejie Fan (medzb@163.com)
Hualu Cui (arren_c@hotmail.com)
Hong Sun (shmad@163.com)
Yongjun Jiang (13998898169@163.com)
Yanan Wang (w_yanan@163.com)
Min Zhao (jyxcmu@163.com)
Amy Sun BS (blueamysun@gmail.com)
Hong Shang (hongshang100@hotmail.com)

Version: 4 Date: 13 July 2015

Author’s response to reviews: see over
Reviewers 1:

Major Compulsory Revisions:

1. Because a major finding of the study is that rapid progression is associated with lower mDC counts, lower maturation markers, and lower IL-12 production, representative flow cytometry plots for IL-12, CD86, and CD1c should be shown for RP vs. TP.

   **Answer**: Thank you for your feedback. We have provided representative flow cytometry plots for IL-12, CD86, and CD1c in Figure 2 according to your advice.

Minor Essential Revisions

1. In the Background, the authors do not clearly present a hypothesis or rationale for evaluating persons with rapid vs. typical progression. This should introduced more clearly in the Background.

   **Answer**: Thank you very much. We have revised the Background and presented a more clearly rationale to evaluate patients with rapid vs. typical progression.

2. In line 120 of the Methods, the markers are all listed as FITC. Were the cells not stained for co-expression of all these markers? If not, the methods need to clarify that the cells were stained for single expression of these markers.

   **Answer**: Thank you very much. No, CD1c+ mDCs were not stained for co-expression of all these markers. As we have mentioned in the Background, CD1c+ mDCs are defined as lineage-negative (including CD3, CD14, CD16, CD19, CD20 and CD56) cells.

3. Lines 127-130 of the Methods need to include fluorochromes for all markers.

   **Answer**: Thank you very much. Sorry for this mistake, and we have added fluorochromes for all markers.

4. Lines 240-246 discuss the rationale behind lower CD1c+ mDC counts in persons with rapid progression, however none of these reasons explains the difference between RP and TP. Why doesn't the decline of CD1c+ mDC equally affect persons with RP and TP? Are mDC less likely to become infected in TP? Does HIV infection cause less CD1c downregulation in TP? Is rapid progression the cause of or the result of lower mDC counts?

   **Answer**: Thank you very much for your kind suggestion. We have modified the Discussion. Several studies have reported that the decrease in CD1c+ mDC counts observed in HIV-1-infected individuals could be due to HIV-1-induced cell death or recruitment to lymphoid organs in order to facilitate the immune system (*The Journal of infectious diseases* 2009, 199(7):1007-1018). While the underlying cause of the faster decline of CD1c+ mDC counts in RPs was unclear, we thought the virus might induce more cell death or recruit more CD1c+ mDCs to lymphoid organs because of
the differences between individuals. Meanwhile, as our study has proved that the patients with low CD1c+ mDC counts were more likely to experience rapid disease progression than those with high CD1c+ mDC counts. Rapid progression is both the cause and the result of lower CD1c+ mDC counts.

5. Minor grammar modifications
Answer: Thank you very much. We have asked BioMed Proofreading, LLC and native English speakers to re-polish the paper and correct grammar modifications.

Discretionary Revisions

1. Table 2 contains somewhat superfluous information with irrelevant statistics. This could be removed from the manuscript.
Answer: Thank you very much. We have removed superfluous information with irrelevant statistics from Table 2.

2. In the Discussion, the authors could elaborate on the implications of the study. I.e., should we implore different therapies in RP vs. TP? Should we treat RP with DC during early infection?
Answer: Thank you very much for your kind suggestion. We have revised the Discussion. We thought that low CD1c+ mDC counts provided important prognostic information that could be used to guide therapy. RPs with low CD1c+ mDC counts might be more likely to benefit from early treatment.

Reviewers 2:

Major Compulsory Revisions

1. The manuscript is difficult to follow due to the poor quality of the written English. Extensive editing is required.
Answer: Thank you very much for your kind suggestion. We have asked BioMed Proofreading, LLC and native English speakers to re-polish the paper to the best of our ability.

2. The data are relevant and the experiments apparently properly designed. Nevertheless, for a full validation of the results, illustrative dot-plots of the flow cytometry analysis should be provided.
Answer: Thank you very much. We have provided representative flow cytometry plots in Figure 2 according to your advice.

3. The discussion should be carefully edited. Some of the statements appear abusive but this may in part result from language problems.
Answer: Thank you very much for your kind suggestion. We have modified some abusive statements and asked BioMed Proofreading, LLC and native English speakers
Further, the patients selection needs to be clarified; 18 out of 29 patients classified as rapid progressors appear too many; was an active selection made to reach these proportions between populations? A follow up of a median of 4 mo is very short, although it is compatible with a rapid progression, but what about cd4 percentage, and the response to therapy? Were they really RP? The consistency of the population of typical progressors inadequate. A description of the evolution of CD4 and viral load, studied as stated in the Methods would be necessary.

Answer: Thank you very much for your kind suggestion. We have described the evolution of CD4+ T cell counts, viral loads, and CD4+ T cell percentages of RPs and TPs, and their responses to therapy in the Results. We have also provided the characteristics in Table 1, and the amendments were highlighted in annotation in the revised manuscript. 18 out of 29 patients were reconfirmed as rapid progressors. Although it seemed like an active selection, we did study 29 consecutive patients to avoid subjective bias. A previous study from our team confirmed the disease progression of MSM in China was faster (J Acquir Immune Defic Syndr. 2013 Apr 1; 62(4): 441-6.). We have also modified the follow-up days as a median of 1149 (862-1297) days.

A point to highlight
We apologize that we forgot two authors who contributed to this paper. One is Min Zhao, who provided funds for our study. The other is Amy Sun, BS, who provided some useful advices on our writing.