Reviewer’s report

Title: Modulation of hepatic PPAR expression during Ft LVS LPS-induced protection from Francisella tularensis LVS infection

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Reviewer: Wangxue Chen

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The manuscript by Dr Mohapatra et al. profiled the hepatic gene expression in a mouse model of intraperitoneal infection with the live vaccine strain of Francisella tularensis LVS (LVS) and the effect of LPS pretreatment on the gene expression profile. The authors found that >3,000 genes were differentially expressed at 48 hours post LVS infection and LPS pretreatment down-regulated many genes associated with inflammation. More importantly, the authors found significant up-regulation of the fatty acid metabolism pathway genes when Gene Set Enrichment Analysis was used.

Although LVS is highly virulent to mice, particularly by the i.p. route, this strain of the pathogen is highly attenuated in humans and in mice by the subcutaneous route. There is little doubt that i.p. LVS infection in mice constitutes an excellent model for studying the pathogenesis of intracellular bacterial infections, similar to intravenous BCG and Listeria monocytogenes infection models. However, its value as a model for human tularemia remains to be determined.

While it is interesting and potentially significant to identify a significant up-regulation of the fatty acid metabolism pathway genes and the expression of PPARalpha and PPARgamma following i.p. LVS infection and LPS pretreatment, the data presented in this manuscript is still preliminary. It is understandable that the authors intentionally avoided presenting any clinical, pathological or bacterial data to reduce the length of their manuscript because these data have been presented in their previous publications. However, it is difficult to get a full appreciation and interpretation of the microarray/qRT-PCR alone without any clinical and bacteriologic data. In addition, the significance of this manuscript is severely diminished by the lack of any functional data to support the potential importance of PPAR-regulated fatty acid metabolism pathway in the pathogenesis of and protection against i.p. LVS challenge. To this extent, even some in vitro experiments would substantially improve the significance of the findings presented in this manuscript.

Minor issues:

Pg 3 (last paragraph): please remove one “i.p.”.

Pg 5 (RNA extraction): Was the whole liver or only segments of liver used for RNA extraction? If liver segments were used, please state how sampling in individual mice was standardized.
Fig. 4: Please clarify the meanings of the significance symbols. Are they significant from different times post LVS challenge or significantly different between LPS and no-LPS treatment at the same time point.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I am an active research on tularemia field with the emphasis on host defense and immunopathogenesis. However, my research has no direct conflict with the subject of this manuscript.