Reviewer's report

Title: Comparative analysis of the human hepatic and adipose tissue transcriptomes during LPS-induced inflammation leads to the identification of differential biological pathways and candidate biomarkers

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Reviewer: Rinke Stienstra

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In this manuscript entitled “Comparative analysis of the human hepatic and adipose tissue transcriptomes during LPS-induced inflammation leads to the identification of differential biological pathways and candidate biomarkers’ Szalowska and colleagues describe the identification of tissue-specific biomarkers using ex vivo LPS treatment of liver and adipose tissue obtained from different donors. In addition to microarray analysis, the authors have confirmed the gene expression changes by performing proteomics. Although the manuscript is of interest, I do have several comments and concerns. The study appears to be well performed and analysed. However, I feel that the current setup, using both female and male donors of various age and BMI and LPS stimulation, makes it very difficult to identify tissue-specific biomarkers that can be indicative of tissue-specific insulin resistance.

Major points

1. Inasmuch quiet some inter-individual variation is observed upon LPS treatment (page 19, TNF# response in liver after LPS treatment), it appears that there is a heterogeneous response. How do the authors explain this phenomenon?

   Why did the authors select LPS to induce inflammation? Is the hepatic TLR4 expression in liver different among the donors used in the study? Is there any difference in TLR4 expression between liver and adipose tissue that might explain the different response seen in liver vs. adipose tissue?

2. Histology/characterization of liver and adipose tissue morphology is lacking. It is not unthinkable that the morphology of the adipose tissue, for example the adipocyte size or the number of macrophages present within the tissue, is different between donors. This might have influenced the LPS-induced gene expression profile and subsequent secretome analysis. Similarly, various degrees of hepatic steatosis among the different donors could have affected the outcome of the study. This information needs to provided.

   Finally, although it will be very difficult to obtain, it would have been much better if the authors had compared liver and adipose tissue secretome of the same donor. Currently, the authors have compared the outcome of LPS-induced gene expression in liver samples from male donors versus adipose tissue obtained from female donors.

3. I find it difficult to interpret figures 1-5. The authors should discuss these
4. Have any of the identified markers been previously linked to adipose tissue inflammation? In addition, what is known about their function and are these proteins mainly derived from adipocytes or the non-adipocyte fraction within the adipose tissue? In other words, what could be their role in adipose tissue?

5. What is the tissue-specific expression profile of the identified potential biomarkers PTX3, MMP1, Serpine1 and CX3CL1? In other words, are these genes specifically expressed by the adipose tissue and not by any other organs/tissues? This can be easily tested. Inasmuch the authors claim that the identified biomarkers might be used for tissue-specific diagnosis of insulin resistance, this piece of information is vital.

6. Is the microarray data publically available?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.