Reviewer's report

Title: A systems biology approach to understand the pathophysiological mechanisms of cardiac pathological hypertrophy associated with rosiglitazone

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Reviewer: Kristiaan Wouters

Reviewer's report:

The manuscript by Verschuren et al. Describes transcriptomic analysis of heart tissue from animals with diet-induced obesity treated with either rosi- or pioglitazone. Remarkably, the authors find large differences between both treatments with respect to the induced transcriptome. They find transcriptional indications of altered substrate utilization with potential roles for PPARα and PGC1α herein.

The current study is interesting and sheds light on the pathways possibly leading to maladaptive cardiac hypertrophy and dysfunction in response to rosiglitazone, but not pioglitazone.

Major Compulsory Revisions:

- Interestingly, although the transcriptome data suggest a shift toward glucose utilization, the carbohydrate cluster seems to be regulated equally between the treatments (Fig. 3D). Can this be explained?

- To what extent are the transcriptomic effects observed in the heart related to direct effects of the TZDs on cardiac gene expression levels? The fact that only 39 and 8 PPARgamma target genes were regulated by respectively Rosi and Pio may suggest otherwise. As already included in the discussion, cardiomyocyte-specific PPARg deletion does not affect Rosi-induced cardiac hypertrophy. As such, processes elsewhere in the body may steer hypertrophy and consequential substrate shifting in the heart. The authors use transcriptional data stratified for plasma glucose levels. I support such a choice to eliminate extra-cardiac factors from influencing the analysis. However, perhaps such differences, if any, can be used to substantiate that the observations are independent from systemic factors? In other words, are conclusions the same when measuring some key genes in the animals with differential plasma glucose (or perhaps other parameters such as FFA, or TG levels)?

Discretionary Revisions

- It can be informative to include a data table including the specific regulation of the individual genes of the processes that are key to the conclusions of the manuscript.

- The phrase “Functional annotation shows that these rosiglitazone-specific effects involving PPAR## and/or PGC1#-controlled genes do at least partly explain the characteristic effects on biological processes Lipid Metabolism, Fatty
Acid Metabolism and Energy Production (Venn diagrams; Figure 4A and B).” is somewhat unclear to me, please rephrase

**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 declare that I have no competing interests'