Reviewer's report

Title: The role of the small intestine in the development of dietary fat-induced obesity and insulin resistance in C57BL/6J mice

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Reviewer: Leslie P Kozak

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Comments on manuscript â## The role of the small intestine in the development of diet-induced obesity and insulin resistance in C57BL/6J mice,â## by Nicole JW deWit et al.

This is a very timely and important study on an organ system vital to the development of diet-induced obesity in B6 mice. Experimentally the study is well designed and molecular analyses of gene expression well done technically. An effort was made to be comprehensive in the bioinformatic analyses. However, the focus on the metabolic, signaling and transcription pathways as well as the biological system has in many respects missed some important insights and over-emphasized others.

It would seem that if one asked, â##How does the intestine contribute to the development of a positive energy balance in DIO?â## Two major systems come to mind, the effects of the intestine on the passage fat into the circulation and the effects of the high fat diet on the synthesis and secretion of gut peptides that regulate food intake. While the issue of nutrition metabolism was dealt with in some detail, in some respects too much detail, the effects of the high fat diet on peptides regulating food intake is almost neglected. Over 11 peptides are synthesized by the intestine (for a comprehensive review see Chaudhri et al. in Phil. Trans R. Society B (2006) 361, 1187-1209.), yet one had to search to find information on a couple. It is important sometimes to provide evidence when expression of a gene is not significantly different, as was done for the PPAR and nuclear receptors. While it is understandable that a lab interested in the PPARs might spend a lot of effort on examining their levels of expression, to this viewer the conclusion would be the changes in these receptors is really insignificant (Table 2), but they hand on the to belief that there are important changes. If there are important changes it is in the question, why do gene targets of PPARs such as Acyl-CoA thioesterases, Cytochrome P-450 a10 show such robust changes in expression? Might there be other transcription factors more important than PPARs. Similarly, too many words are spent on genes associated with chronic inflammation, yet the short periods of time on a high fat diet would not be expected to induced high levels of expression of genes of inflammation.

The recommendation of this reviewer is that it is essential to consider the points made here to revise the presentation of results and discussion.
Another essential recommendation: A small, but important request concerns the absence of important data that should be added. In the methods a protocol was described for the analysis of feces, but no data was presented in the manuscript. Was there a difference in the energy content of the feces and was there a difference in energy intake between mice on high and low fat?

**What next?:** Accept after minor essential revisions

**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