Reviewer's report

Title: Role of Receptor-Interacting Protein 140 in Human Fat Cells

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Reviewer: Margareta Jernas

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This paper, performed by Mejhert et al, is devoted to elucidate if receptor-interacting protein 140 (RIP140) might be involved in the regulation of the subcutaneous fat mass in humans and if RIP140 had similar function in human white adipocytes as in murine adipocytes.

The nuclear receptor corepressor RIP140 is shown in mice to be expressed in several organs, however the mRNA levels in white adipose tissue (WAT) are higher than in other metabolically active tissues. The physiological function of RIP140 has been tested in RIP140 knock out (RIPKO) mice, and it seems to play an important role in energy homeostasis in mice.

It has recently been reported that RIP140 mRNA and protein levels are decreased in human visceral WAT of morbidly obese as compared to lean subjects, implying that human RIP140 may, just as in rodent orthologue, regulate adipose tissue metabolism.

This present study demonstrates mRNA levels of RIP-140 in human subcutaneous WAT from women with a wide range in BMI, and after weight reduction. Furthermore, it demonstrates RIP-140 mRNA knocked down siRNA in in vitro differentiated adipocytes, and the impact on glucose transport and mRNA levels of target genes determined.

The authors show that RIP140 mRNA levels in subcutaneous WAT were decreased in obese compared to lean women and increased by weight-loss. Associations between RIP140 mRNA levels in subcutaneous WAT and mtDNA copy number have also been investigated. RIP140 expression increased during adipocyte differentiation in vitro and was higher in isolated adipocytes compared to corresponding pieces of WAT. Knock down of RIP140 increased basal glucose transport and mRNA levels of glucose transporter 4 and uncoupling protein-1. On the basis of these results, the authors conclude that increased levels of human RIP140 in subcutaneous WAT of lean subjects may contribute to economize on energy stores.

The study is elegant, well-performed and original. However, some minor issues could be addressed:

1) Page 4-5. The authors describe that RIP140 is expressed in mice organs that is metabolically active tissues, such as liver, muscle and brown adipose tissue (BAT). It could be of interest to add in what human organs RIP140 so far has
been reported to be expressed.

2) Page 6-15. Cohort 2. Reference 10 describes that the subjects involved in the study are women, and this could be added in this sentence, describing cohort 2. Do you have any data on male subjects, so you know if there is a difference between genders in the RIP140 expression?

3) Page 12-7. The authors show significant decreased RIP140 mRNA levels in subcutaneous WAT in obese compared with lean subjects, and they also show that RIP140 mRNA level is decreased in visceral WAT of obese subjects. Do you have any data if there are significant differences of RIP140 mRNA levels between visceral and subcutaneous WAT, within both lean and obese subjects? Visceral adipose tissue is significantly more metabolically active than subcutaneous fat tissue, and in the effort to study the regulation of RIP140, it could be of interest to add.

4) Page 14-8. The authors say; "RIP140 is more abundantly expressed in isolated fat cells than intact WAT". In this kind of study, data would be useful but not essential to provide a comparative expression of RIP140 in whole adipose tissue, isolated adipocytes and the stroma vascular fraction (SVF) with suitable expression. Since SVF composition changes during obesity settlement and after weight reduction, as shown in various recent papers, it is a point which could be valuable.

5) Page 15-5. Some more comment could be spent in the discussion and the sentence; in 3T3-L1 adipocytes, the effects of RIP-140 on glucose uptake is at least partly mediated via the transcription factor ERR alpha (add estrogen-related receptor, not just abbreviation). This transcription factor is not mentioned before in the manuscript and there could be additional comment around evidence why ERR alpha, at least partly, effects RIP-140.

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

**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