Reviewer's report

Title: AMPD1: A Novel Therapeutic Target for Reversing Insulin Resistance

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Reviewer: Richard L Sabina

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The authors have conducted a generally well-designed study in AMPD1-deficient mice and have generated an interesting set of data to indicate that AMPD may be a novel therapeutic target for combating insulin resistance.

- Minor Essential Revisions

1. Although data presented clearly indicate that p-AMPK levels are higher in skeletal muscles of A1(-/-) mice, do the authors have any other data to indicate that AMPK activity is also elevated? A corollary to this comment is to ask for more information about the specificity of the reagent that was used to generate the phosphorylation data. I feel that this may be important information for the reader because, for example, while it is well established that phosphorylation at alpha-Thr(172) is linked to AMPK activation, phosphorylation at alpha-Ser(485/491) has been shown to antagonize AMPK activation in the rat heart.

2. Methods, under “Glucose and insulin tolerance,” first paragraph: “administered” is mis-spelled.

3. “Results and discussion” should be changed to “Results,” as the authors later preface the Discussion section with “Discussion.”

4. Third paragraph under Discussion: A comma is needed between “As expected” and “fat content.” Also, the sentence beginning with this text is a bit long with many commas. Perhaps it could be broken up into two sentences.

5. Fourth paragraph under Discussion: “faction” should be changed to “fraction”

6. First sentence under Conclusions does not make sense and should be re-written for clarity:

“In conclusion, the results of this study validate AMP deaminase as potential new drug target for the amelioration of insulin resistance treat one of the underlying causes of the metabolic syndrome and Type II diabetes.”

- Discretionary Revisions

This reviewer is unaware of any isoform-specific inhibitors of AMPD, and until these become available, if at all, it would be interesting to know if
AMPD2-deficient mice and AMPD3-deficient mice that the authors have also developed respond similarly to this experimental setting. While I am not suggesting that these studies be conducted at this point, perhaps the authors could address this if they feel that such investigation warrants future studies.

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.