Reviewer's report

Title: DNA methylation of the glucagon-like peptide 1 receptor (GLP1R) in human pancreatic islets

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Reviewer: Xin Gao

Reviewer's report:

This is an interesting paper that describes a possible new mechanism for DNA methylation of the GLP1R on the development of T2DM. In the manuscript, the authors used pancreatic islets from 55 non-diabetic and 10 type 2 diabetic donors to investigate the levels of DNA methylation of GLP1R and gene expression, HbA1c, age and BMI. The authors showed that while BMI and HbA1c are positively associated, gene expression is negatively associated with DNA methylation of GLP1R (CpG -376) in human pancreatic islets. Supplementary table 1 in the manuscript showed that degree of DNA methylation is very low (below 10%) and there is only a slight increased DNA methylation (CpG -376 and +199/205) in T2DM compared with non-diabetic donors.

Another important shortcoming of this manuscript is the insufficient data to support the conclusion.

Therefore, I suggest the following experiments to address the possible mechanism.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached):

1) Conduct western blot analysis to examine the protein expression of the gene GLP1R and MeCP2.

2) Correlation between the degree of DNA methylation of CpG site +199/205 of the GLP1R gene in pancreatic islets and A) GLP1R mRNA expression, B) BMI and C) HbA1c levels in all individuals of the studied cohort.

3) In the discussion section of the manuscript, the present study suggests that hyperglycemia and/or obesity may affect DNA methylation of GLP1R, rather than DNA methylation of GLP1R influencing hyperglycemia. This discussion should be expanded.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore):

1. Measure the levels of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy) in the pancreatic islets and plasma levels of homocysteine in T2DM and non-diabetic donors. This may indicate if the levels of methyl group donors affect the DNA methylaton of GLP1R.

2. Measure DNA methylase levels and activity or the mRNA and protein levels of selected DNA methylases in the islet of the two groups. This may indicate the
mechanism of DNA methylation of GLP1R.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Fig 1B/ 3 figure legends should add:* p<0.05. **??

**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.