

**Dear Dr. Ma:**

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "A new role for ceramide in hypoxia and insulin resistance". (ID:53647).

We have studied reviewers' comments carefully and have made revision which marked in red in the paper. We have tried our best to revise our manuscript to make it more comprehensive according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration. The main corrections in the paper and the responds to the reviewers' comments are as following:

**Reviewer #1:**

**Response to comment:** The authors reviewed hypoxia and ceramide, leading to insulin resistance. The manuscript provided enough information.

**Response:** we are pleased to your favorable comments and sincerely thank you for this.

**Reviewer #2:**

**Response to comment 1:** If clinical data were presented, this review would be more attractive to clinicians. For example, ceramide concentration and insulin resistance. Clinical situation or conditions were not clear.

**Response:** we added some new clinical trials, which marked in red in our manuscript. Unfortunately, there is no consistent ceramide concentration in clinic due to the small sample size and different ceramide detection methods.

**Response to comment 2:** The authors stated that hypoxia increased concentration of ceramide. They presented intestinal hypoxia due to obese.

**What situation did the authors imagine as intestinal “intestinal hypoxia due to obese”?**

**Response :** Hypoxia-inducible factors (HIFs) are a family of transcription factors activated by hypoxia. A study revealed that the relationship between intestinal hypoxia and obesity contributes to hepatic steatosis(Nat Med,2017,23(11):1298-1308 ). In intestinal epithelial cells, HIF-2 $\alpha$  is activated and accumulates by hypoxia in HFD mice. Furthermore high-fat diet (HFD)-induced obesity and hepatic steatosis and insulin sensitivity have improved in intestine-specific HIF-2 $\alpha$  ablation mice. In addition, treatment with a pharmacological specific inhibitor of HIF-2 $\alpha$  (PT2385) or inhibitor of NEU3 (N-acetyl-2,3-didehydro-N-acetyl-neuraminic acid, DANA or naringin) lessens serum levels of ceramides, reduces obesity and fatty liver and enhances insulin sensitivity. Hence, obesity can lead to intestine hypoxia.

**Response to comment 3: Does that mean that intestinal membrane becomes hypoxic as the weight gains?**

**Response :** According to existent research, intestinal mucous membrane is becoming hypoxic if weight gains resulting in pathological changes such as obesity, insulin resistance or hepatic steatosis

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Jing Gong